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THE EISENMENGER SYNDROME

OR PULMONARY HYPERTENSION WITH REVERSED CENTRAL SHUNT*

BY

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Distinctive Characteristics of Individual Members of the Eisenmenger Group

Patent Ductus.—(1) The catheter passed through the duct more easily than through any other central communication between the two circulations. It did so in 90% of cases, and usually took an anticlockwise course to enter the descending aorta. (2) The shunt was wholly reversed far more frequently (50%) than with other defects. (3) Patent ductus was the only lesion which was occasionally associated with no shunt in either direction. (4) Differential oxygen desaturation between right brachial and femoral samples was pathognomonic of patent ductus, and occurred in all but two cases in which there was no shunt in either direction. The oxygen saturation of samples from the right brachial artery averaged 89.6% (range 81 to 96%), and from the descending aorta or femoral artery 77.1% (range 65 to 88%).

Aorto-pulmonary Septal Defect.—(1) When the catheter passed through the defect it entered the ascending aorta from the pulmonary artery. (2) In other respects the findings were similar to those of patent ductus with bidirectional shunt but no differential desaturation.

Eisenmenger's Complex.—(1) Passage of the catheter via the defect (28%) into the ascending aorta followed a characteristic medial course as in Fallot's tetralogy. (2) An appreciable left-to-right shunt at ventricular level, as described by Bing *et al.* (1947), could be detected in all but two cases, in both of which the diagnosis was subsequently proved at necropsy. (3) Pulmonary artery samples were always between 5 and 20% less saturated than aortic or arterial samples.

Single Ventricle.—In all respects but one these cases resembled Eisenmenger's complex. The increase in oxygen saturation at ventricular level averaged 16%. The one distinctive feature was the similarity of aortic (or arterial), pulmonary artery, and ventricular samples. The arterial oxygen saturation was no lower than in other members of the Eisenmenger group, averaging 82%. Three such cases were proved at necropsy.

Transposition of the Great Vessels.—These cases also resembled Eisenmenger's complex in all major respects but one. The distinctive feature was the higher oxygen saturation of samples from the pulmonary artery compared with those from the aorta and right ventricle. In the three cases studied the difference was 32, 17, and 5%. The rise in oxygen saturation at ventricular level averaged 20%. Three cases in the series resembled Eisenmenger's complex in all respects except that the catheter took a left anterolateral convex course as it entered the ascending aorta (Plate, Fig. I, *Journal*, September 20, facing p. 709), characteristic of one type of corrected transposition. The pulmonary artery is not readily entered in such cases.

Persistent Truncus.—There were three characteristic features in the two cases studied. (1) The physiological situation was similar to that in aorto-pulmonary septal defect with the addition of a second left-to-right shunt at ventricular level. As the catheter passed from the right atrium, through the right ventricle, into the truncus, the oxygen saturation of respective samples rose first by 10 and 12.5%, and then by a further 10 and 14%. (2) The catheter entered the pulmonary arteries from the "aorta," instead of vice versa as in aorto-pulmonary septal defect. (3) Samples from the "aorta" and pulmonary arteries were identical.

Atrial Septal Defect.—(1) The catheter passed through the defect in two-thirds of 18 proved cases. (2) The pulmonary artery pressure was less than the systemic pressure by an average of 27/34 mm. Hg in 70% of the cases; in 10% it was higher; and in the remainder about the same. When mean pressures were similar the pulse pressure was usually greater in the pulmonary artery, the systolic pressure being higher and the diastolic lower than in the systemic arteries. Agents affecting pulmonary or systemic flow or resistance selectively usually altered the pressure relationship between the two circulations. (3) A direct shunt at atrial level was demonstrated in 84% of the cases, right atrial samples being on the average 13% more saturated than samples from the superior vena cava (range 6 to 21%). (4) The oxygen saturation of left atrial samples averaged 81% in the eight cases in which they were obtained (range 72 to 88). Left ventricular samples were similar when secured, and arterial samples likewise (average 82% saturated; range 70 to 88%).

Persistent Ostium Primum.—The physiological findings in four cases could not be distinguished from a combination of low atrial septal defect and ventricular septal defect, there being bidirectional shunts at both atrial and ventricular levels. The rise in oxygen saturation averaged 10% in the right atrium and 7.5% in the right ventricle. The lie of the catheter when it entered the aorta was similar in both groups to that in Fallot's tetralogy and Eisenmenger's complex.

Common Atrioventricular Canal.—A single proved case that came to necropsy had virtually both a single atrium and a single ventricle. The rise in oxygen saturation resulting from the left-to-right component of the bidirectional shunt occurred at atrial level and measured 23%. Samples from the common ventricle, pulmonary artery, and femoral artery were similar at around 80% saturated.

Anomalous Pulmonary Venous Drainage.—As a cause of the Eisenmenger reaction both total and hemianomalous pulmonary venous drainage must be rare, for no case was recognized amongst the 127 studied in this paper. One of

*Conclusion of the Croonian Lectures delivered before the Royal College of Physicians of London on May 15, 1958. See last week's *Journal* (p. 701) for first part.

the additional necropsies, however, previously diagnosed as an ostium secundum type of atrial septal defect, was found to have total anomalous pulmonary venous drainage into a relatively small vein joining a locally dilated right superior vena cava. This female infant died at the age of 1 year with a pulmonary artery pressure of 105/60. No wedge pressure was recorded, but the pulmonary venous pressure must have been high in view of the small calibre of the single vein joining the superior vena cava, and this must have excited reactive pulmonary hypertension as described by Johnson *et al.* (1958) in four similar cases in which the single anomalous vein carrying all the blood from the lungs was stenosed where it joined the inferior vena cava or porta hepatis.

Dye-dilution Curves

The best method of identifying the site of the reversed shunt in Eisenmenger's syndrome is to inject a suitable dye first into the root of the pulmonary artery, then into the right ventricle, and finally into the superior vena cava, and to record in each instance its time–concentration curve in the systemic arteries by means of a modified ear oximeter or cuvette as described by Swan *et al.* (1953). In cyanotic cases the most suitable dye is undoubtedly Fox green (cardio-green) in view of its dissimilarity from reduced haemoglobin.

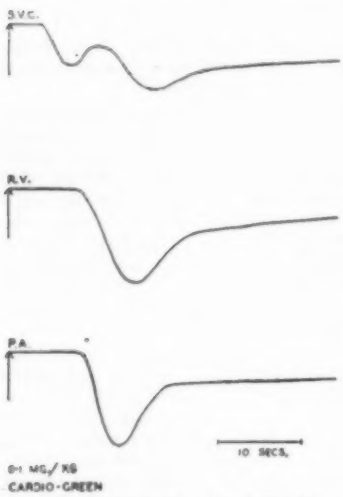

FIG. 10.—Dye-concentration curves from the radial artery after injecting cardio-green first into the superior vena cava, then into the right ventricle, and finally into the pulmonary artery: the double hump in the top tracing is due to the early appearance (time) of the dye when it has been injected proximal to the reversed shunt. Eisenmenger's syndrome associated with an atrial septal defect in a man aged 30.

A reversed shunt is demonstrated by the early arrival of dye at the detection point (ear or brachial artery), the substance having short-circuited the lungs. As this first wave of the dye-concentration curve begins to wane a second hump appears, representing dye that has passed through the lungs in normal time (Fig. 10). In the case illustrated the double hump so formed appeared only when the dye was injected into the superior vena cava, proving that the reversed shunt was at atrial level.

While offering a highly satisfactory method of determining the site of a reversed shunt in Eisenmenger's syndrome, dye-concentration curves do not distinguish between individual members of each group, at least when the shunt is at atrial or ventricular level.

Angiocardiography

Selective angiocardiography may also resolve the site of a reversed shunt, and not infrequently distinguishes between individual members of each group. With atrial septal defect, for example, diodone appears in the aorta and pulmonary artery more or less simultaneously only when injected into the superior vena cava (or high right atrium), not when injected into the right ventricle or pulmonary artery. Angiocardiography usually distinguishes patent ductus, transposition, corrected transposition, and persistent truncus from ventricular septal defect, and retrograde aortography separates aorto-pulmonary window from ventricular septal defect (Fig. 11). Selective angiocardiograms, however, give no information about pressure, and reversed shunts are encouraged by transient overfilling of the chamber into which the contrast medium is injected; moreover, the danger of an overdose of *x* rays may limit the number of angiocardiograms to which a patient should be exposed, especially after cardiac catheterization. Dye-dilution curves have no such disadvantage.

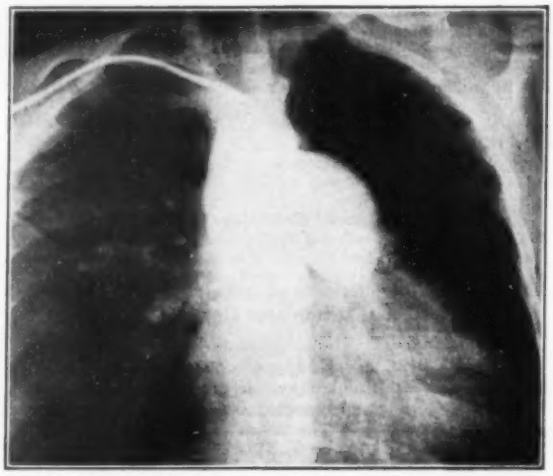

FIG. 11.—Retrograde aortogram in a case of Eisenmenger's syndrome associated with an aorto-pulmonary window (with acknowledgments to Mr. Walter Somerville).

Necropsy Findings

Death occurred in 18 of the 127 cases of Eisenmenger's syndrome, and necropsy was carried out in 15 of them. Details of 38 additional necropsies of cases studied during life were sent to me by many kind colleagues in Britain, making a total of 53.

Mode of Death

The cause of death was known in 42 of these cases. *Haemoptysis* was the commonest natural cause, and was responsible in 29%; it was usually profuse and caused death within a few minutes, as in Eisenmenger's case. The nature of the collapse has already been discussed. Necropsy proved that the cause of the haemoptysis was usually pulmonary infarction from arterial thrombosis. In some cases, however, this was not established, and rupture of a thin-walled dilated arteriole immediately distal to the end of a thick muscular artery, as described by Dammann and Ferencz (1956) and Edwards (1957), could not be excluded. In a case described by Selzer and Lewis (1949) death was due to rupture of an aneurysm of the pulmonary artery, but this is most unusual.

Surgical repair of the defect was responsible for 26% of the fatal cases, and *congestive failure* for 17%; death was abrupt, presumably from *ventricular fibrillation*, in 14%. No other single cause, such as bacterial endocarditis, cerebral abscess, cerebral thrombosis, or pregnancy accounted for more than 5%.

Accuracy of Diagnosis

Of the 15 necropsied cases in the series fully analysed, the clinical diagnosis was wholly correct in nine, wholly wrong in two, and correct in respect of the site of the shunt but wrong in respect of the nature of the defect in four. A 40% error after full investigation is embarrassing; it was no less in the 38 borrowed cases nor in published reports in the literature. What is even worse is the high frequency of false pathological reports. The last two patients that died, for example, were diagnosed clinically as ? total anomalous pulmonary venous drainage in one case, and persistent ostium primum with bidirectional shunt

at atrial and ventricular levels in the other; the pathological reports from the hospitals where they died concluded that the first had nothing more than a simple atrial septal defect of the secundum type, and that the second had a single ventricle with intact atrial septum.

When a pathologist more accustomed to congenital heart disease examined the specimens he showed conclusively that the first had total anomalous pulmonary venous drainage into a normal right superior vena cava and the second a common atrioventricular canal with a functionally single atrium and virtually single ventricle. This is salutary experience, and emphasizes the very great care and knowledge that are needed to work out the precise physiological and anatomical situation in the Eisenmenger syndrome.

Size of the Defect

It has been stated, not infrequently, that the size of the defect is less important than the pulmonary vascular resistance in determining the Eisenmenger syndrome. This is a half-truth, for the size of the defect may very well determine the pulmonary vascular resistance. A major difficulty here is that measurements of the size of the defect vary considerably according to the circumstances under which the measurements are made. Surgical estimates in the live heart during repair work, for example, are always larger than post-mortem measurements; and post-mortem measurements are larger when made immediately after death, when the heart is fresh, than when made subsequently after the heart has been fixed. Discrepancies relating to the size of defects in reported cases, therefore, are bound to arise. Nevertheless, the following statements are secure. (1) No case of patent ductus with the Eisenmenger reaction has ever been reported with a lumen less than 5 mm. in diameter. (2) No case of Eisenmenger's complex has ever been reported with a ventricular septal defect less than 1 cm. across. (3) The size of an atrial septal defect has relatively little bearing on the presence or absence of a high pulmonary vascular resistance, and varies freely between 3 and 8 cm. in both uncomplicated and pulmonary hypertensive groups.

The size of the defect in the 53 necropsies under review is given in Table VI, where it is compared with the common size of defects in uncomplicated cases as given by Abbott

TABLE VI.—*Size of Communication*

	Normal Resistance. Usual Range	Eisenmenger Range
Duct.	0·1 to 1·0 cm.	0·7 to 1·5 cm.
V.S.D.	0·1 to 2·0 cm.	1·5 to 3·0 cm.
A.S.D.	3 to 8 cm.	3 to 8 cm.

(1927), Taussig (1947), and Brown (1950). The figures agree fairly closely with those given for ventricular septal defect by Selzer and Laqueur (1951).

Ducts under 1 cm. across with the Eisenmenger reaction were short, and the smallest were specifically stated to have had no length. Aorto-pulmonary windows are usually large—up to 5 cm. or so in their long diameter—but probably need to be no larger than the smaller ducts, since they have no length. That ventricular septal defects averaged twice the diameter of the ducts is attributed to the fact that aorto-pulmonary shunts continue throughout the whole cardiac cycle, whereas interventricular shunts are believed to be chiefly systolic.

As pointed out by Selzer and Laqueur (1951), there is no gradual transition between a large ventricular septal defect and single ventricle. The former rarely, if ever, exceeds 3 cm. in diameter and occupies no more than 10% of the septal area in a fully grown heart; the latter has a ridge where the septum should be, but that is all. Single ventricles are always complicated by pulmonary stenosis, as in the six cases described by Campbell *et al.* (1953), or by a high pulmonary vascular resistance (Rogers and Edwards, 1951). Transposition of the great vessels may be associated, but is obviously unimportant physiologically.

Elastic Arteries

Atheroma of the large elastic arteries was common, as reported by all writers, and as originally described by Eisenmenger. Secondary thrombosis and pulmonary infarction were increasingly common after the age of 20.

Of exceptional interest is the state of the elastic fibres in the main trunk of the pulmonary artery itself. Heath (1958) pointed out that in the foetus and newborn babe these elastic fibres were long and densely packed as in the aorta. As the pulmonary artery pressure falls the fibres seem to break up, shorten, and become loosely arranged, so that they no longer resemble the aortic pattern. Heath found that sections of the pulmonary artery in Eisenmenger's complex and patent ductus with reversed shunt always resembled the foetal (or aortic) pattern, whereas in atrial septal defect with pulmonary hypertension and reversed shunt, and in all forms of pulmonary hypertension known to be acquired, the appearances were more like those in a normal pulmonary artery. He concluded that pulmonary hypertension in the Eisenmenger syndrome must be present from birth with ventricular septal defect and patent ductus, but must be acquired in atrial septal defect—at least in the great majority of cases. It should be understood that the function of elastic fibres is to prevent distension from high pressure.

Muscular Arteries

In Eisenmenger's complex pulmonary arteries with a diameter of less than 1 mm. have a thick muscular media very similar to their structure in the foetus. Civin and Edwards (1950, 1951) suggested that it was the persistence of the foetal type of muscular artery that was responsible for the high resistance, and that this saved infants with large ventricular septal defects from dying as a result of an inadequate blood flow into the aorta. In their own words, "the pulmonary vascular bed of patients with the Eisenmenger complex who survive infancy maintains its foetal function." They assumed that the thick muscular arteries of the foetus were responsible for the high pulmonary vascular resistance necessary to deflect blood from the right ventricle away from the lungs into the descending aorta via the ductus arteriosus.

Thick muscular arteries have been demonstrated also in children with a single ventricle (Edwards and Chamberlin, 1951; Heath, 1957), large patent ductus (Whitaker *et al.*, 1955), and all other members of the Eisenmenger group (Edwards, 1957).

During the first two years of life the intima usually remains normal; thereafter, however, and with varying degree and tempo from case to case, progressive intimal fibrosis develops (Edwards, 1957). This is the pulmonary vascular disease that has been regarded by some as the chief cause of Eisenmenger's syndrome—for example, Whitaker (1958). Subscribers to this hypothesis do not say how these intimal changes have come about.

Arterioles

The arterioles of the lung are vessels less than 100 μ in diameter, and consist of endothelium, a single elastic layer, and adventitia; they are not supplied with muscle. Dammann and Ferencz (1956) support Edwards in his belief that the arterioles are usually thin-walled and dilated in Eisenmenger's syndrome, and that thick-walled vessels within the usually accepted compass of an arteriole are really muscular arteries in a state of contraction, an interpretation which has been extended by Short (1957) to embrace larger arteries with thick muscular coats.

The Overriding Aorta

The following observations may clarify the position in respect of the override.

1. Ventricular septal defect is but one of a total of some 12 kinds of communication between the two circulations, all of which may be complicated by a high pulmonary vascular

resistance and reversed shunt of similar magnitude. An overriding aorta or its physiological equivalent is absent in seven of these conditions.

2. When the pulmonary vascular resistance is high the arterial oxygen saturation averages close to 80% in transposition with ventricular septal defect, persistent truncus, single ventricle, the so-called Taussig–Bing syndrome (in which the pulmonary artery is supposed to be overriding the defect in cases of transposition), and Eisenmenger's complex with or without apparent override.

3. Eisenmenger's complex with all the classical features may be associated with a defect in the muscular part of the interventricular septum as in the cases described by Weiss (1927) and Heath *et al.* (1956). There can be no overriding of the aorta in such instances.

Experimental Physio-pathology

The reaction of the pulmonary circulation in Eisenmenger's syndrome to pulmonary vasoconstrictor and vasodilator drugs seemed worth investigating.

Oxygen

In adults and in the great majority of children over the age of 5, 100% oxygen fails to lower the pulmonary artery pressure (Fig. 12) or to influence the magnitude of the shunt, as first demonstrated by Burchell *et al.* (1950).

On the other hand, breathing 10% oxygen raises the pulmonary vascular resistance and increases the reversed shunt, at least in cases with patent ductus (Burchell *et al.*, 1953).

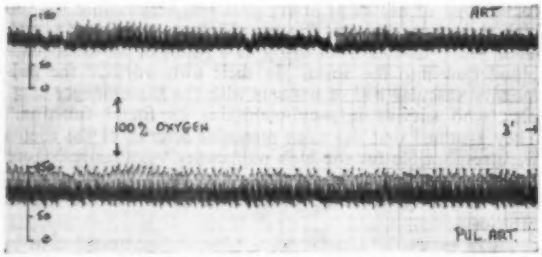

FIG. 12.—Failure of 100% oxygen to lower the pulmonary artery pressure in a case of Eisenmenger's complex.

In infants under 2 and occasionally in small children, when intimal fibrosis in the pulmonary circulation is negligible, breathing 100% oxygen almost halves the resistance and increases the pulmonary blood flow (Edwards, 1957).

Acetylcholine

Acetylcholine, when injected direct into the pulmonary artery in a dose of 0.5 to 1.5 mg., is an ideal selective pulmonary vasodilator, for this quantity is usually inactivated by cholinesterase by the time it reaches the systemic circulation (Wood *et al.*, 1957).

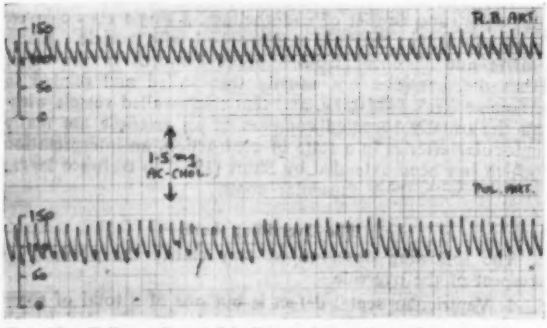

FIG. 13.—Failure of acetylcholine to lower the pulmonary artery pressure in a case of Eisenmenger's complex.

When severe pulmonary hypertension was primary, or due to mitral stenosis or cor pulmonale, acetylcholine lowered the pulmonary artery pressure and resistance, and raised the cardiac output in 85% of cases (Wood, 1958). In 13 cases of Eisenmenger's syndrome, however, no such effect could be demonstrated in a single instance (Fig. 13). The youngest patient in the series, however, was 5 years old, and it is probable that infants under 2, without intimal fibrosis, would react differently. This belief is founded on the different response of these infants to 100% oxygen, as described previously, and on the fact that acetylcholine lowers the pulmonary vascular resistance sharply in the foetal lung (Dawes, 1958).

Negative reactions to tolazoline hydrochloride (" priscol ") and aminophylline have also been without exception in cases of Eisenmenger's syndrome in patients over the age of 5.

Protective Effect of Stenosis

One case of aorto-pulmonary septal defect had moderate stenosis of the origin of the right branch of the pulmonary artery (Fig. 14). The pressure fell from the systemic level of 85/55 mm. Hg in the pulmonary artery to 60/40 beyond the stricture in the right branch. The nature of the defect

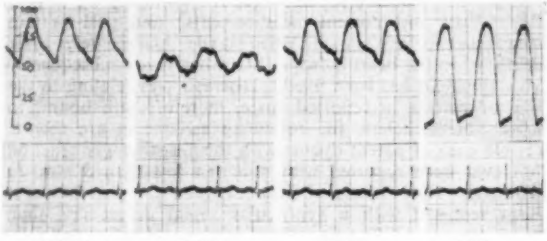

FIG. 14.—Pressure pulses in a case of Eisenmenger's syndrome associated with an aorto-pulmonary septal defect and stenosis of the right pulmonary artery near its origin.

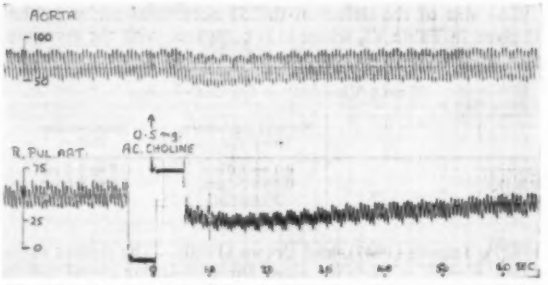

FIG. 15.—Pressure pulse from right pulmonary artery beyond the stricture, showing a marked reduction of pressure following the injection of acetylcholine. The pulmonary vessels have been protected by the stenosis and are functioning normally.

was demonstrated by passing the catheter through it. When acetylcholine was injected into the right pulmonary artery the pressure fell sharply from 55/38 to 30/18 (Fig. 15). It is true that the child was also the youngest in the series investigated, being only 3 years old, but that does not alter the conclusion that vessels which are protected from extreme pulmonary hypertension, or which have not had time to develop serious intimal fibrosis secondary to the hypertension, respond briskly to acetylcholine. This disposes of the idea that there is anything fundamentally wrong with the pulmonary vessels at birth in the Eisenmenger syndrome.

This functional evidence stands solidly side by side with the anatomical observation that when the origin of the left pulmonary artery is atresic in Eisenmenger's syndrome its distal branches and muscular arteries, which are not subjected to high pressure, are perfectly normal, whereas the vessels on the other side have all the features characteristic of Eisenmenger's complex (McKim and Wiglesworth, 1954).

Similar anatomical evidence was provided by Civin and Edwards (1950) in a case of large ventricular septal defect (2.5 cm.) with marked overriding of the aorta associated with mild infundibular stenosis of the fibrous diaphragm type, the orifice being 1.5 cm. in diameter and above the level of the shunt. This man died from carcinoma of the bladder at the age of 47, and at necropsy the pulmonary vascular tree was normal.

The protective effect of stenosis is the basis of modern surgical therapy in the Eisenmenger group (Civin and Edwards, 1950; Dammann and Ferencz, 1956).

Course and Prognosis

As previously stated, the Eisenmenger syndrome is commonly established at birth or during the first two years of life when the shunt is aorto-pulmonary or interventricular, but is typically acquired when the shunt is interatrial. In the present series, for example, cyanosis dated from infancy in 80% of those with ventricular septal defect, but did not start until adult life in 92% of those with atrial septal defect. The onset of reversed shunt in patent ductus is more difficult to establish, because differential cyanosis is usually overlooked. Aorto-pulmonary septal defects, however, behave like ventricular septal defects.

The majority of those who have studied the Eisenmenger syndrome at all closely have come to the same conclusion. Thus 8 out of 13 acceptable cases of Eisenmenger's complex collected from the literature by Selzer and Laqueur (1951) dated their cyanosis from infancy, as did at least 50% of 29 clinical cases studied by Donzelot *et al.* (1949), and all except 2 out of 20 cases reported by Kohout *et al.* (1955).

As a general rule neither cyanosis nor breathlessness changes appreciably during childhood or adolescence, but deterioration sets in sooner or later in adult life. The onset of recurrent haemoptysis may signal the downward trend, which is due in many cases to the development of thrombo-obstructive lesions.

The average age of natural death in the 18 fatal cases in this series and the 38 additional cases from elsewhere, omitting three which died in infancy, was 33 for both aorto-pulmonary and ventricular defects, and 36 for atrial septal defects. The cases in which death occurred in infancy included one severe ostium primum, one common atrio-ventricular canal with what was virtually cor biloculare, and one total anomalous pulmonary venous drainage into a stenosed vessel joining the right superior vena cava.

The maximum age reached was 65 for both the ventricular and the atrial cases, and 55 for the ducts.

The downhill course was usually punctuated with haemoptyses, which when severe sometimes caused sudden collapse and death within a few minutes, as previously described.

Bacterial endocarditis occurred in only 5% when it was responsible for death; cerebral abscess from paradoxical embolism occurred once and proved fatal; cerebral thrombosis also occurred in one case, but was not fatal. An appreciable number (14%) died abruptly, presumably from ventricular fibrillation.

As many as 26% of the fatal cases died from a surgical attempt to repair the defect, mostly from ligation of a patent ductus.

Patients who survive these risks develop congestive heart failure sooner or later, and this was the cause of death in 17% of the fatal cases.

Treatment

Medical treatment aims at preventing secondary thrombo-obstructive lesions by means of permanent anticoagulants, such as phenindione ("dindevan"). Pulmonary vasodilators, such as tolazoline, aminophylline, and reserpine, fail to lower the pulmonary vascular resistance, and do not influence the course of the disease (Rudolph *et al.*, 1958). Small venesections, repeated from time to time, may be helpful in cases with gross polycythaemia, but should be undertaken very slowly and with the utmost vigilance. Heart failure requires the usual remedies.

Surgical repair of the defect has been responsible in recent years for more deaths in the Eisenmenger syndrome than any other agent except haemoptysis. Ellis *et al.* (1956) stated that the surgical mortality in cases with reversed shunt through a patent ductus was 56%, and Anderson *et al.* (1956), after reviewing 45 such cases in the literature, could find only four good results. Similar fatalities and poor results in the survivors are now taking place with repair of ventricular septal defect and atrial septal defect complicated by pulmonary hypertension and bidirectional shunt.

Direct repair of a defect, without the special preparation that is discussed below, is justified only when it can be predicted with confidence that its closure must result in a fall of pulmonary blood pressure because a hyperkinetic factor of sufficient magnitude has been eliminated. In practice this prediction can be made when the pulmonary blood flow is at least twice the systemic flow at rest, and the pulmonary vascular resistance does not exceed 10 units (800 dynes sec./cm.^{5}). Borderline cases have pulmonary/systemic flow ratios of 1.75 to 2, and resistances of 10 to 12 units. No case with a pulmonary blood flow less than 1.75 times the systemic flow or with a resistance over 12 units should have the defect repaired in the ordinary way, whether the shunt is reversed, direct, or bidirectional.

Observance of this law since its introduction on theoretical grounds in 1950 has resulted in a mortality rate of zero for cases of patent ductus in this class. Several of them just within the limits outlined, and with samples from the femoral artery having oxygen saturations between 82 and 85%, have been cured by duct ligation. In these instances the pulmonary artery pressure fell, and the systemic pressure rose, when the duct was compressed manually. A year later the pulmonary vascular resistance was either normal or close to normal. In cases unsuitable for duct ligation identical pulmonary artery and aortic blood pressures do not separate favourably when the duct is manually occluded. Precisely the same criteria must apply to cases with interventricular or interatrial shunt.

Synthesis

The cardiac output of the newborn babe is about 0.5 l./min. (Prec and Cassels, 1955), and is presumably much the same in the foetus at term; if the situation is similar to that in the lamb, about 0.1 l./min. passes through the pulmonary circulation (Dawes *et al.*, 1954). Since the mean pulmonary artery pressure is the same as the aortic, about 50 mm. Hg at birth, the foetal pulmonary vascular resistance must be about 500 units (40,000 dynes sec./cm.^{5}).

During the first three hours after birth a reversed shunt through a patent ductus is invariable (Eldridge *et al.*, 1954); from 3 to 72 hours after birth the shunt may be direct, bidirectional, or reversed (Eldridge *et al.*, 1954; Prec and Cassels, 1955; Amoroso *et al.*, 1958); and by the end of the third day the duct is usually closed. It follows that in newborn infants the pulmonary vascular resistance is more or less the same as the systemic—that is, about 100 units (800 dynes sec./cm.^{5})—for, as previously stated, the cardiac output is about 0.5 l./min., and the mean pressure around 50 mm. Hg.

Within a remarkably short time after birth, then, probably within a few minutes of independent life, a pulmonary vascular resistance around 500 units falls to about 100. Four questions clamour for an answer: (1) What is the cause of the fantastic pulmonary vascular resistance in the foetus? (2) Why does it drop so precipitously at birth? (3) Why is the rapid fall halted temporarily more or less at systemic level? (4) What is responsible for the subsequent slower decline to normal?

In the correct answer to these four questions lies the secret of the Eisenmenger syndrome.

An answer to the first has been offered by Alan Burton (1958), who points out that resistance to flow in a tube is

greatly increased by kinking the vessel. In the fully developed foetus the pulmonary vessels are as long as they are a few minutes after birth, but since the lung is completely collapsed they must be coiled up, or kinked in innumerable places, and Burton has demonstrated their "gnarled" appearance. It can be readily understood that vessels in such a state may be highly resistant to flow.

The answer to the second question follows. As the lungs expand the vessels uncoil: as the kinks straighten out the resistance falls; as the blood begins to flow through the lungs the vessels must dilate, and this also lowers the resistance (Williams, 1954); the blood that fills up the pulmonary vascular bed acts as a natural scaffolding and encourages further expansion (Jäykkä, 1957). Stepwise, and in a matter of a minute or so, and aided by lusty cries, the lungs are fully expanded (Lind and Wegelius, 1956), the vessels are wholly unfurled, and the pulmonary vascular resistance is at systemic level, at least five times lower than *in utero*.

The difficulty about accepting this explanation is that the resistance falls precipitously only when the lungs are inflated with any kind of gas, and does not do so at all when the lungs are distended with saline (Dawes *et al.*, 1953). What is clear, however, is that the initial steep fall in resistance is closely associated with full expansion of the lung.

An alternative suggestion that the astronomical resistance in the foetus is due to hypoxic vasoconstriction is untenable in view of its equally rapid fall when the lungs are inflated with nitrogen (Dawes *et al.*, 1953). Nor can the thick muscular arteries of the foetus be blamed for the high resistance *in utero*, because they could hardly be expected to change their structure in a few minutes; nor in fact do they do so, as the microscope shows clearly enough.

This brings us to the third question: Why is the rapid fall in resistance at birth temporarily halted at systemic level? This may well be a function of the thick muscular arteries just mentioned. In the foetus these have developed in relation to the systemic pressure to which they have been subjected, and, as shown by Dawes (1958), they are also in a state of active vasoconstriction, which can be released by acetylcholine. After birth a powerful right ventricle, as big and strong as the left, pumps its contents into a system of vessels which differs little from the systemic circulation; it is only natural, therefore, that pulmonary and systemic resistances should be similar.

During the first day of life, then, the physiological and anatomical findings are identical with Eisenmenger's syndrome associated with patent ductus. Two events of great importance must now be considered: the first is the relaxing effect of an increased alveolar oxygen tension on the tone of the muscular arteries; the second is the closure of the ductus arteriosus. Before the duct closes, release of vasoconstrictor tone in the muscular arteries is met by an increased flow from aorta to pulmonary artery, and this hyperkinetic factor tends to maintain the pulmonary artery pressure at systemic level. When the duct closes, and this hyperkinetic factor is eliminated, release of vasoconstrictor tone lowers the pulmonary artery pressure, and the approach to normal adult physiology begins. Just how quickly this goal is reached depends on the speed of involution of the muscular arteries. Edwards (1957) states that complete involution takes about three months.

The factors responsible for the final change to the adult arrangement, and so for the answer to the fourth question, are believed to be as follows. (1) As the pressure falls in the pulmonary circulation vasoconstrictor tone is diminished, for muscular arteries react to increased pressure by contracting and to decreased pressure by relaxing (Bayliss, 1902). This local response of the muscular arteries to any change in pressure must increase that change in either direction. (2) As the resistance declines the pulmonary blood flow increases. This must dilate the vessels and so lower the resistance still further (Williams, 1954). (3) As the pressure falls the muscular arteries atrophy and so diminish their resistance to flow.

The Eisenmenger Reaction

All that is necessary to prevent these natural forces from lowering the pulmonary vascular resistance to normal is a sufficient increase of flow to keep the pressure at systemic level. Any large aorto-pulmonary or interventricular communication will do just this, and the higher the resistance the less increase of flow necessary to maintain the pressure. If the pressure is maintained pulmonary vasoconstrictor tone must remain high, and the muscular arteries will not atrophy. This is the situation in the Eisenmenger syndrome, and it will be understood that it must be established at birth if the defect is large enough.

If the defect is not quite critical, however, the shunt flow at rest may not be sufficient to maintain the pressure at systemic level, and the forces acting in the opposite direction may win or partially win the competition. Once the resistance falls appreciably much larger flows are necessary to maintain high pressure. This brings us to the peculiar behaviour of cases with interatrial shunts.

Pulmonary Hypertension in Atrial Septal Defect

It was stated in the introduction that no hypothesis explaining Eisenmenger's syndrome was tenable unless it provided a solution to the question why cases with large atrial septal defect behaved differently. The simple answer that in atrial septal defect there is no "common ejectile force" will not do, because with a potentially large left-to-right interatrial shunt the powerful right ventricle in the newborn babe would certainly maintain the pulmonary artery pressure at or above systemic level, and so prevent both relaxation and subsequent involution of the muscular arteries. Since in fact this relaxation and involution must take place in cases with atrial septal defect, it follows that *there can be no interatrial shunt during the critical period.* That an atrial septal defect may not function for an appreciable time after birth is not at all unlikely, for the two great causes of a left-to-right interatrial shunt are a larger volume of blood returning to the left atrium than to the right (so that the shunt is self-perpetuating), and a lower resistance to diastolic filling on the part of the right ventricle compared with the left. Now, before the shunt operates it is obvious that the self-perpetuating factor inherent in an increased pulmonary blood flow may be disregarded, so that only filling resistance need be considered.

Resistance to filling or diastolic myocardial tone is presumably related to the mass of relaxed muscle that must stretch in response to the filling pressure. When the mass of the two ventricles is similar—as in many cases of Fallot's tetralogy, simple pulmonary stenosis, and Eisenmenger's complex, for example—little difference between the diastolic tone in each ventricle can be detected, and if an atrial septal defect happens to be present it may permit of no appreciable shunt in either direction. Many examples of this state of interatrial balance have been encountered in the conditions mentioned. At birth the mass of each ventricle is roughly the same, and it is probable, therefore, that diastolic myocardial tone in each ventricle is also the same. If this is true there should be no left-to-right shunt of any magnitude through an atrial septal defect at this time.

Just how soon the right ventricle involutes sufficiently to permit a shunt large enough to maintain pulmonary hypertension is unknown, but serial electrocardiograms in normal infants strongly support the view that involution is slow, far slower than involution of the muscular pulmonary arteries. In practice, also, uncomplicated atrial septal defect is rarely diagnosed in infancy, and the pulmonary systolic murmur so characteristic of an increased pulmonary blood flow is not usually heard "until the child is well past the neonatal period" (Nadas, 1957).

If this reasoning is correct, and the pulmonary vascular resistance falls to normal before the interatrial shunt gains much momentum, it becomes very difficult for the Eisen-

menger reaction to develop later, for once the pulmonary vessels are fully involuted an increased pulmonary blood flow is met by further reduction in the pulmonary vascular resistance, as in the normal individual, so that flows of 24 litres per minute may be associated with a resistance of about one-third normal (0.33 unit), and a mean pulmonary artery pressure only 8 mm. Hg higher than the left atrial pressure.

Subsequent Course of the Eisenmenger Syndrome

During the first two years of life pulmonary hypertension at systemic level maintains the hypertrophied and contracted state of the muscular pulmonary arteries, and the high pressure type of elastic tissue in the larger elastic arteries. During this period the muscular arteries are capable of relaxing, at least in response to increased alveolar oxygen tension. Whether or not they relax in response to acetylcholine, aminophylline, tolazoline, or reserpine is as yet unknown, but they may well do so: if the defect were repaired at this time, and the infant treated in an oxygen tent with pulmonary vasodilators, the pressure should fall, and if it did so the pulmonary vascular resistance should gradually diminish as a result of release of local vasomotor tone and involution of the muscular arteries.

After about two years of continuous pulmonary hypertension, however, reactive intimal fibrosis tends to obliterate the lumen of the muscular arteries, and they no longer respond to vasodilating agents. The obliterative process presents a solid anatomical obstruction to flow and replaces vasoconstriction as the chief cause of the high pulmonary vascular resistance. The pulmonary blood flow at this stage may be no greater than the systemic flow, and repairing the defect is without benefit. There are borderline cases, however, in which the pulmonary blood flow is twice the systemic flow and the pulmonary vascular resistance under 10 units, and in these there is still a good chance that repairing the defect may lower the pulmonary artery pressure enough to promote the involutionary changes that must lead back to health.

As life advances, usually between the ages of 20 and 30, thrombo-obstructive lesions develop in the larger pulmonary arteries which increase the resistance considerably and herald the beginning of the downhill course. These lesions may be prevented in good measure by permanent anticoagulant therapy. Just what part thrombosis plays in the production of the intimal fibrosis of the muscular arteries mentioned previously is controversial.

Cases of atrial septal defect with a low pulmonary vascular resistance may continue to have large pulmonary blood flows until they die from congestive failure between the ages of 50 and 75. About 10% of any large series of cases of atrial septal defect confirm this statement. An increased pulmonary blood flow *per se* does not, therefore, cause obliterative pulmonary vascular disease. The Eisenmenger reaction in atrial septal defect develops gradually, however, in a relatively small number of cases in which a powerful hyperkinetic factor comes into being before complete involution and relaxation of the muscular pulmonary arteries has taken place. In childhood the pulmonary vascular resistance in this group is not as low as it should be, so that flows of 16 to 24 litres per minute cause hyperkinetic pulmonary hypertension. If the resistance is 2 units, for example, a pulmonary blood flow of 24 litres per minute must result in a pulmonary blood pressure of about 70/30 mm. Hg (mean 48). Progressive intimal fibrosis and late thrombo-obstructive lesions then develop as complications of the hypertension, and as the obliterative process continues the resistance increases, the pressure rises further, and a vicious circle is inaugurated. In the end the physiological situation is similar to that in other members of the Eisenmenger group. Such cases are usually curable if the defect is repaired before the resistance reaches 10 units, and when the pulmonary blood flow is still at least twice the systemic flow.

Protective Effect of Pulmonary Stenosis

The evidence that pulmonary stenosis protects the pulmonary circulation from developing obliterative endarteritis is overwhelming. As suggested by Edwards (1950) and as practised by Dammann and Ferencz (1956), artificial stenosis of the pulmonary artery may be created surgically in cases of Eisenmenger's syndrome in order to lower the pulmonary artery pressure and so initiate the involutionary cycle. Just how long it may be wise to maintain the stenosis before repairing the defect remains to be seen, but the post-operative course of cases of mitral stenosis with extreme reactive pulmonary hypertension suggests that a year or two should be sufficient.

Summary

Eisenmenger's syndrome may be defined as pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at aorto-pulmonary, ventricular, or atrial level.

It may be caused by patent ductus, aorto-pulmonary septal defect, persistent truncus, transposition with ventricular septal defect, corrected transposition with ventricular septal defect, ventricular septal defect, single ventricle, common atrioventricular canal, persistent ostium primum, atrial septal defect, single atrium, and hemianomalous or total anomalous pulmonary venous drainage into the right side of the heart.

These conditions have in common a large communication between the two circulations exceeding 0.7 cm. in diameter when aorto-pulmonary, 1.5 cm. when interventricular, and 3 cm. when interatrial. If the pulmonary vascular resistance were normal, such defects would cause a pulmonary/systemic flow ratio of at least 3.5, and the usual range would be 4 to 6.

The clinical and physiological features of 127 cases of the Eisenmenger syndrome are analysed and presented with special emphasis on the distinguishing characteristics of each type.

A total of 53 necropsies from cases well investigated during life were studied in relation to the clinical and physiological data. Thirty-eight of these do not belong to the series, but were used to check certain interpretations that needed more pathological support.

When the shunt was aorto-pulmonary or interventricular the Eisenmenger reaction was initiated and maintained from birth in at least 80% of the cases; when the shunt was interatrial the reaction was chiefly acquired in 90%.

The key to the physio-pathology of Eisenmenger's syndrome lies in the behaviour and structure of the pulmonary circulation in the foetus, newborn babe, and during the first three months of infancy.

The fantastic resistance of the foetal pulmonary circulation is attributed to the contorted state of the vessels in fully collapsed lungs.

The thick muscular arteries of the foetus and newborn babe represent a functional and structural reaction to high pressure.

Expansion of the lung after birth unfurls the pulmonary vessels and lowers the resistance precipitously to around systemic level (about 100 units).

Subsequent reduction of the pulmonary artery pressure is gradual, and depends on the relaxing effect of an increased alveolar oxygen tension on vasomotor tone, the inhibition of vasomotor tone that results from a fall in pressure *per se*, early closure of the ductus preventing

an adverse hyperkinetic factor, and gradual involution of the muscular pulmonary arteries.

In Eisenmenger's syndrome with aorto-pulmonary or interventricular shunt, this favourable cycle is prevented by a powerful hyperkinetic factor which maintains the pulmonary artery pressure at systemic level. So long as pulmonary hypertension is maintained vasoconstrictor tone is not inhibited and the muscular pulmonary arteries do not involute.

Obliterative pulmonary vascular disease due to reactive "endarteritis fibrosa" is secondary and is rarely found in infancy.

Thrombo-obstructive lesions are relatively late and may not be demonstrable before adult life.

The different behaviour of cases with atrial septal defect may be explained by the relatively slow involution of the right ventricle after birth. The pulmonary vascular resistance may well fall to normal before right ventricular diastolic tone is reduced sufficiently to allow a critical interatrial shunt, and, once the resistance is truly normal, flows up to 24 litres per minute do not cause pulmonary hypertension.

The practical application of these observations to the treatment of the Eisenmenger syndrome is discussed.

This analysis was begun in 1948 and two attempts at synthesis were made previously; the first in conjunction with Dr. J. B. Lowe in 1950, the second with Dr. H. Gilmour in 1953; and, though both attempts proved unsatisfactory owing to lack of sufficient data, I want to express my great indebtedness to these two colleagues.

Details of necropsies on cases well investigated during life were sent to me by Drs. I. M. Anderson, D. Evan Bedford, Wallace Brigden, Maurice Campbell, William Evans, Frances Gardner, C. J. Gavey, Ronald Gibson, Frederick Jackson, and Walter Somerville; I am very grateful to all of them for their trouble and generosity.

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LOCAL TREATMENT OF BRONCHIAL ASTHMA WITH HYDROCORTISONE POWDER

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The fact that bronchial asthma can be greatly improved by systemic treatment with cortisone and its derivatives is well established. This treatment, however, demands high dosage and thus has the disadvantage of causing cortical atrophy, and of other risks. Its continued use must therefore be limited to patients whose life is endangered by the asthma or where invalidism is threatening.

If a similar therapeutic effect could be achieved by local instead of systemic treatment the dosage could be expected to be much lower, and the risks connected with high dosage would be avoided. A local effect of hydrocortisone has been well known for some time in allergic disorders of the eye and of the skin. In hay-fever a similar effect has been reported more recently and has been confirmed (Herxheimer and McAllen, 1956; Godfrey, Maunsell, and Pearson, 1957; Lake, Logan, and Peters, 1957; Morris-Owen and Truelove, 1958; Findeisen, 1958). Some of these reports include a number of cases in which pollen asthma was present and which were benefited by the treatment. Apart from

these, reports on the local treatment of bronchial asthma with cortisone derivatives are scanty, and, in their conclusions, tentative only.

In this paper we report a number of therapeutic trials undertaken at different centres with the aim of contributing to this question.

Methods

Although the method of selecting patients differed in the three places of trial (London, Cardiff, and Berlin), the treatment was always the same. The patients were advised to inhale one capsule of micronized hydrocortisone snuff from a powder inhaler. A capsule containing 15 mg. of hydrocortisone and 85 mg. of lactose was placed in this inhaler; half of the contents of a capsule was inhaled orally in the morning and half in the evening. The dose of 15 mg. was chosen on the assumption that only a small part of this amount would be distributed systemically and that this part would be well below the body's own hydrocortisone production, which has since been shown to be about 14 mg. a day (Cope and Black, 1958). In many cases the patient served as his own control. In a few cases he was given hydrocortisone powder for a certain time (two weeks), followed by a similar period without powder; in most cases the hydrocortisone period was followed or preceded by an equal period of placebo snuff. In one group no attempt at control was made, and the groups of controlled patients and others will be reported separately.

The greatest difficulty was the selection of patients for the trial. Only those whose condition was a chronic one and moderately severe could be used—that is, the condition had to be fairly uniform throughout the year and severe enough to require continuous treatment. In addition, patients must have been under observation for some years, so that the variations in their condition were well known to the medical observer. Such patients are comparatively rare, as those with frequent and violent ups and downs must be excluded. Their exclusion is an absolute necessity for a trial like this, because violent spontaneous variations might be attributed to the trial substance. But even if patients are selected who conform to the conditions mentioned, there is no safeguard against intercurrent upper respiratory infections with their almost unavoidable temporary deterioration and subsequent improvement, which may mask the influence of the trial substance.

The investigation was started first at University College Hospital with the selection of a group of 12 patients, most of whom we had known for a number of years, and whose condition was stable. They were all under continuous standard treatment, usually on antihistamine drugs at night, sometimes combined with ephedrine or aminophylline during the day. As a stand-by the patients used inhalations of isoprenaline; the number of inhalations required by them during an average day and an average night was fairly constant, so that a change in the condition would be immediately reflected by a change in the number of inhalations. We were fairly confident that these patients would permit a good if provisional impression of the efficiency of the snuff. The patients in this group acted as their own controls.

The second group, containing 53 patients, was formed at Cardiff. It consisted of chronic cases—some of the allergic type and some of the infective type. Nineteen patients were controlled—that is, they had placebo capsules at some time or other, often for several periods—and 34 were uncontrolled—that is, no attempt was made to find out whether they were better or worse without the snuff. Four patients in the controlled group had only mild perennial asthma, but it became severe seasonally. All four of them were mould-sensitive.

The third group, comprising 14 patients, was selected in Berlin after some experience had been gained with the previous groups. They were chronic asthmatics of moderate severity, and in all but three its allergic character was certain.

In every patient the presence or absence of hypersecretion was noted. It was regarded as present if the patient continually had viscous sputum with difficulty of expectoration and therefore required potassium iodide as an expectorant at regular intervals. Patients who required potassium iodide only after acute exacerbations of their asthma are not included in this category.

Results (Table I)

First Group.—Five of the 12 patients were better with the snuff than without it. Their condition had improved so much that other anti-asthmatic medication was required only occasionally. In three others the improvement was moderate: the symptoms were definitely less severe, but other anti-asthmatic remedies were still required, though not so much as before. In the remaining four the result was plainly negative. Of the five considerably improved patients, two had hypersecretion, and another, who had one of the rare "dry" asthmas, showed an extremely impressive improvement. She had been known to us for 12 years, and her history of perennial asthma with peaks in April and August had been longer. She had required frequent injections of adrenaline, these being replaced later by isoprenaline inhalations. A few years ago her condition gradually deteriorated, and she was put on maintenance doses of corticotrophin. She never expectorated any mucus except during rare and short periods of upper respiratory infection. When she was put on hydrocortisone snuff she was soon able to leave off corticotrophin and the frequent isoprenaline inhalations. At the time of writing she was free of asthmatic symptoms with 10 mg. of hydrocortisone snuff a day.

TABLE I.—*Results of Treated Cases*

Patient	Age and Sex	Age at Onset of Asthma	Skin Tests	History of Allergy	Hypersecretion	Result of Treatment
London (12):						
Be	44 M	20	Pos.	Pos.	No	Neg.
Cr	28 M	2	,,	,,	Yes	Pos. +
God	30 M	8	Neg.	Neg.	No	Neg.
Goo*	37 F	20	Pos.	Pos.	,,	Pos. + +
Ha	36 M	17	,,	,,	,,	Pos. +
La	31 M	23	,,	,,	Yes	Neg.
Le	26 M	2	,,	,,	No	Pos. + +
Li	29 F	25	,,	,,	,,	Pos. + +
Ru	53 M	4	,,	,,	,,	Pos. +
Sw	51 M	35	,,	,,	Yes	Pos. + +
Wo†	43 M	34	,,	,,	,,	Pos. + +
Ra	31	3	,,	,,	,,	Neg.
Cardiff (19):						
Al	26 F	22	Neg.	Neg.	No	Pos. + +
An	54 F	51	,,	,,	Yes	Neg.
Ba	31 F	2	Pos.	Pos.	,,	Pos. + +
Ha	60 F	46	Neg.	Neg.	,,	Pos. + +
Je	32 M	3	Pos.	Pos.	No	Pos. + +
Jo	39 F	24	,,	,,	,,	Pos. + +
Ke	45 F	32	,,	Neg.	,,	Pos. + +
Le	30 F	17	,,	Pos.	,,	Pos. +
Lo	48 F	43	Neg.	Neg.	Yes	Pos. + +
Ma	59 F	53	,,	,,	,,	Pos. +
O'N	74 F	69	Pos.	,,	,,	Neg.
Pe	27 F	5	Pos.	Pos.	No	Pos. + +
Ric	37 M	12	,,	,,	,,	Pos. + +
Ria	49 F	16	,,	,,	Yes	Neg.
Sc*	27 M	3	,,	,,	No	Pos. + +
Si	58 F	38	,,	,,	Yes	Pos. + +
Th	54 F	51	Neg.	Neg.	No	Neg.
Zo	58 F	49	,,	,,	Yes	Pos. + +
Xi	60 F	23	Pos.	Pos.	No	Pos. + +
Berlin (14):						
Ca	50 F	29	,,	,,	,,	Pos. + +
El	37 F	4	Neg.	Neg.	,,	Pos. + +
En	23 M	13	Pos.	Pos.	Yes	Neg.
Fo	30 M	5	,,	,,	No	Pos. + +
Gro	24 F	13	,,	?	Yes	Pos. + +
Ha	53 F	41	,,	Pos.	,,	Neg.
Hu*	26 M	23	,,	Neg.	No	Pos. + +
Ka	52 M	15	,,	?	,,	Pos. + +
Kl	31 F	8	,,	Pos.	Yes	Pos. + +
La	41 M	9	Neg.	Neg.	,,	Neg.
Le	22 F	19	,,	,,	,,	Neg.
Ra	22 F	4	Pos.	Pos.	No	Pos. + +
Sc	32 M	7	,,	?	,,	Pos. + +
So	15 M	13	,,	Pos.	,,	Pos. + +

Pos. + + = Considerable improvement. Pos. + = moderate improvement.
* "Dry" asthma.
† Relapsed after being on placebo for two months.

Second Group.—Of the 34 uncontrolled cases, 15 showed or reported an improvement which was judged to be moderate. Often this improvement did not last long and was followed by a respiratory infection and deterioration which took a long time to subside. As no control was possible in these cases, we do not regard them as evidence for the efficacy of the snuff. Of the 19 controlled cases, 13 showed a considerable improvement, in two the improvement was only moderate, and in four there was no improvement. The four patients with seasonal mould allergy are among those with considerable improvement. They were free of symptoms so long as they took the powder. A fifth patient with a very long history of asthma belonged to the dry type, and he also became completely symptom-free. His asthma was so severe that his chest had become deformed and his nutritional state impaired. It was most surprising to see that he no longer required any antispasmodic treatment.

Third Group.—Of the 14 patients, 10 improved considerably; five of them had no symptoms so long as they took the snuff, whilst the other five still had to use antispasmodics, though much less than before. Of the four not improved two belonged to the infective type. Only two of the improved patients had hypersecretion and continued to require potassium iodide. The patient with dry asthma improved a great deal.

Discussion

Although more than two-thirds of our patients have benefited from the treatment, the interpretation of this result requires caution. These patients were not average asthmatics, but a selected group. Many of them were selected because, according to our initial experience, they were likely to respond to the treatment. In contrast to these, the 34 patients who formed the uncontrolled part of the Cardiff experiment were unselected patients. Here the number of failures (19) exceeds the number of patients improved (15), and it is by no means certain that all the positive cases would have been proved positive if they had been in a controlled trial. It follows that this treatment cannot be expected to help the average chronic asthmatic but only certain types, and our investigation has aimed at defining these types as clearly as possible. From Tables II and III it can be seen that we have treated more allergic (33) than infective (12) cases, and that 82% improved in the allergic group as against 50% in the infective group. If we divide our patients into those with hypersecretion and those without, we find that of the 19 patients with hypersecretion only 53% improved, whereas 89% of the 26 patients without hypersecretion showed an improvement.

TABLE II.—*Results Separated for Allergic and Infective Asthma*

	Total	Improved	Unimproved
Allergic asthma	33	27 (82%)	6 (18%)
Infective asthma	12	6 (50%)	6 (50%)

TABLE III.—*Results Separated for Asthma With and Without Hypersecretion*

	Improved		Unimproved	
Patients with hypersecretion				
Allergic	6	(55%)	5	(45%)
Infective	4	(50%)	4	(50%)
Total ..	10	(53%)	9	(47%)
Patients without hypersecretion				
Allergic	21	(95%)	1	(5%)
Infective	2	(50%)	2	(50%)
Total ..	23	(89%)	3	(11%)

Although our figures are too small to permit definite conclusions, they show that the allergic type is more likely to respond than the infective type, and that the presence of hypersecretion is a handicap to the success of the treatment. The allergic type without hypersecretion is likely to do best: there was only one failure in 22. Our experience with the three completely "dry" asthmatics is in accordance with this. The improvement of these three patients in spite of their long history was particularly impressive, because their condition was far more severe than that of the average patient in our trial. In the presence of hypersecretion, however, only half of the patients improved, whether of the infective or of the allergic type. As hypersecretion is more frequent in the infective type, the less favourable response in this type may be due to the hypersecretion. There are too few patients in the group of infective type without hypersecretion to be certain on this point.

Only a few earlier experimental observations in this field are on record. Foulds *et al.* (1955) in a preliminary communication reported an uncontrolled trial of 15 patients with hydrocortisone snuff, of whom 12 improved. Herxheimer and McAllen (1956) have observed that, in 4 out of 10 hay-fever patients who also suffered from pollen asthma, the asthma disappeared after nasal insufflation of hydrocortisone snuff, and they assumed that this was because the snuff was inhaled into the bronchi. Morris-Owen and Truelove (1958) have made similar observations. Brockbank and Pengelly (1958) reported improvement in 17 out of 24 asthmatics with hydrocortisone snuff, but prednisolone snuff had no effect in six out of seven patients. Franklin *et al.* (1958) have also reported success with topical hydrocortisone, given as a suspension, in a majority of patients. These two groups of authors do not specify the type of asthmatic patient used in their studies. For this reason it is not possible to compare our results with theirs.

Our experience shows that the result of topical treatment in any group of asthmatics will mainly depend on the type of asthma involved. Originally we had hoped that the topical treatment of bronchial asthma might replace steroid systemic therapy in most cases and might thus avoid the dangers of continuous large systemic maintenance doses. This hope has not materialized. Only a minority of patients appear to be benefited by corticoids given topically.

It is particularly disappointing that the hypersecretory type, which is normally more difficult to treat, does not respond well. The reason for this is not clear. One might think that the blockage of many bronchi and bronchioli may prevent the action of the corticoid snuff, or that the mucus covering the mucous membrane may prevent its action. If the mucus is the principal obstacle, it should be possible to achieve success by its removal or reduction. In order to test this we have attempted to decrease the hypersecretion in four severe cases by systemic prednisone, and then to replace the systemic prednisone gradually by local hydrocortisone. In three of these cases, however, this substitution was not successful: three of the patients became gradually worse on reducing systemic prednisone from 10-12.5 mg. a day to 5 mg. a day or lower, and the previous systemic maintenance doses had to be resumed. This negative outcome is in contrast to the positive result of Franklin *et al.* (1958) in six out of seven cases. However, these authors have used a prednisolone suspension and not hydrocortisone snuff in their cases, and their type of patient may have been different from ours. Further experiments will be needed to elucidate this question.

Summary

A total of 79 chronic asthmatic patients were treated with hydrocortisone powder, 45 of them in a controlled trial.

In 33 of these 45 patients a definite improvement of symptoms occurred. This improvement was seen mainly in patients with evidence of allergic aetiology and in those without hypersecretion.

Improvement was seen to a much less extent in infective asthma than in allergic asthma.

Cases of "dry" asthma responded dramatically.

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BRONCHIAL ASTHMA AND CHRONIC BRONCHITIS TREATED WITH HYDROCORTISONE ACETATE INHALATIONS

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Foulds *et al.* (1955) reported good results in 12 out of 15 patients with asthma who were treated with inhalations of hydrocortisone acetate in fine-particle powder. Brockbank and Pengelly (1958) and Helm and Heyworth (1958) carried out short-term controlled trials which showed that a statistically significant number of patients responded well to these inhalations as compared with the number responding to inhalations of placebo powder.

The purpose of the present paper is to record the results of two years' experience with inhalations of hydrocortisone acetate powder in patients with asthma and wheezy bronchitis and to suggest some indications for this treatment. An attempt has also been made to estimate the quantity of "inhaled" powder which enters the stomach rather than the tracheo-bronchial tree.

Material

The patients selected had all suffered from asthma or wheezy bronchitis for at least one year, and their condition had been severe enough to necessitate periods off work, except in two patients whose asthma was almost entirely nocturnal. There were 25 men and 28 women treated. The ages varied between 15 and 61 years, the mean being 40 years.

Groups and Definitions.—Bronchial infection was judged to be present if the sputum contained macroscopic pus. Where necessary the pus was examined microscopically to differentiate pus due to eosinophils rather than true pus cells. For convenience of analysis the cases were divided into five groups: (1) recurrent acute asthma without significant bronchial infection; (2) chronic asthma without significant bronchial infection; (3) recurrent acute asthma with significant intermittent infection; (4) chronic asthma with significant intermittent infection but little persistent sputum; and (5) chronic wheezy bronchitis with significant persistent or intermittent infection and more than ¼ oz. (7 ml.) of sputum daily. The main difference between patients in groups 4 and 5 was in regard to the daily quantity of sputum, but infection tended to be a more prominent feature in group 5 than in group 4.

Method

All patients with significant bronchial infection when first seen were admitted to hospital for investigation and treatment with antibiotics and routine antispasmodic drugs before receiving hydrocortisone inhalations, and patients whose signs and symptoms cleared completely concurrent with elimination of pus from the sputum were excluded. If the sputum rapidly became purulent again on stopping the antibiotic it was restarted and the patient remained on a small maintenance dose while starting hydrocortisone inhalations. All patients with infection were instructed to start antibiotics again should an exacerbation of infection occur while remaining on the inhalations after discharge from hospital. Patients with severe asthma (without infection) when first seen were admitted to hospital and were treated routinely with antispasmodic drugs for a few days before inhalations were given.

The patients inhaled fine hydrocortisone acetate powder from a "pabracort" inhaler, the powder being in capsules containing 15 mg. of hydrocortisone and 75 mg. of lactose powder, both being ground fine to a mean particle size of 5 microns. The initial dose varied between one capsule three times a day and one capsule daily given as half a capsule twice daily according to the severity of the wheezing at the beginning of treatment. The dose was reduced to the minimum maintenance necessary as soon as improvement occurred. Most patients were able to reduce the dose to half a capsule twice daily within the first week; this was the usual maintenance dose, although some needed to continue with two capsules daily, and some were able to reduce to half a capsule daily.

Treatment was stopped entirely in patients with recurrent acute asthma once the attack had been relieved for a week, and they were provided with capsules and instructed to restart at the onset of symptoms in a dose of between one and three capsules daily according to the severity of the attack. All patients were given any other routine treatment necessary, and this often included an antispasmodic drug before the hydrocortisone inhalation in order to facilitate deep inspiration. Those who responded well but later relapsed while continuing treatment were given prednisone by mouth in addition to the inhalations.

Patients who had failed to make any definite improvement during two weeks' treatment with inhalations were assessed as failures and the treatment was stopped.

Follow-up and Assessment of Results

The assessment of the results of treatment was made on both subjective and objective grounds. All patients had had prolonged routine treatment before starting the inhalations, and this provided a baseline from which the changes in signs and symptoms could be judged. All patients were seen by the same physician at monthly intervals or less while remaining on the treatment. Special attention was paid to the symptoms of dyspnoea and tightness of the chest, to exercise tolerance, and to the need for bronchodilator drugs. On physical examination the presence or absence of wheeze was noted and, if present, was assessed as slight, moderate, or severe on each visit.

Patients with significant bronchial infection (groups 3, 4, and 5) were instructed to bring a 24-hour specimen of sputum for inspection on each visit.

The results of the inhalation of hydrocortisone acetate powder in bronchial asthma and wheezy bronchitis are shown in the Table.

Of the 53 patients, 43 (81%) improved on hydrocortisone inhalations, whereas 10 (19%) were no better. Of the 43 patients who improved, 13 (30%) relapsed after periods of 1 to 11 months, whereas 30 (70%) maintained the improvement up to the time of writing for between two months and two years. The best results were obtained in group 1 patients with recurrent acute asthma without infection, whereas the results in group 5 patients with wheezy bronchitis were disappointing.

Complications.—There were no definite complications in the present series, but one man had mild dyspepsia for a few weeks which may have been due to the hydrocortisone.

Several patients put on weight, which was probably due partly to improved health and partly to the effects of hydrocortisone absorption.

Table of Results

Group	No.	Not Improved	Improved	Improved but later Relapsed	Maintained Improvement to Present	Duration of Improvement in Patients	
						Relapsing	Remaining Well
1	12	1	11	1	10	9 months	2 months to 2 years. Mean 1 year
2	18	3	15	5	10	4–11 months. Mean 7 mths.	3–18 months. Mean 8 months
3	7	0	7	2	4	2–5 months. Mean 3½ mths.	2½–11 months. Mean 5 months
4	7	0	7	4	4	1–6 months. Mean 3 mths.	3–18 months. Mean 11 mths.
5	9	6	3	1	2	2 months	1–4 months. Mean 2½ mths.
Total	53	10	43	13	30		

Case Histories

Group 1.—A 20-year-old girl had had eczema, hay-fever, and intermittent asthma all her life. In March, 1955, she started a course of mixed inhalant desensitization, but after a short period of apparent improvement she became worse than ever in the autumn, and had three months of almost continuous wheezing which was little affected by routine measures. She was then started on hydrocortisone inhalations, and the symptoms rapidly resolved. She continued to use the inhalations on about two days out of three in a dose of one capsule daily for the next two years, and remained very much improved during this period, with only six weeks off work, compared with eight months off work in the previous two years.

Group 3.—A 37-year-old woman with no relevant family history had begun to get asthma at the age of 13. The attacks remained fairly mild and were precipitated mainly by emotion or exertion until the age of 18, when she had several years of freedom. At the age of 25 she again began to get attacks of asthma following colds and bronchitis. In November, 1956, she had a cold followed by persistent bronchitis with fever and purulent sputum: the infection finally cleared after several courses of antibiotics, but she continued to have attacks of wheezing, especially at night, and failed to respond to energetic routine measures, including antispasmodic and antihistamine drugs. After two weeks of continued night attacks with little sleep, she started hydrocortisone powder inhalations: she took one capsule in the afternoon and another in the evening. She slept well for the first time that night and had no further wheezing while carrying on with the inhalations for the next two weeks. After stopping the inhalations she remained free of asthma until a further attack following a cold one year later. This attack was again relieved by a few days of hydrocortisone inhalations.

Group 4.—A 61-year-old woman with no relevant family history had begun to have a slight cough and sputum at the age of 18. At 38 she first began to have severe wheezing attacks with no known precipitating factors: the attacks were intermittent for many years, but at the age of 58 the wheezing became almost continuous, with intermittent severe attacks necessitating weeks in bed. Finally she was confined to bed for three months with chronic status asthmaticus, and was admitted to hospital. On admission she was acutely short of breath and had a marked expiratory wheeze: she had 2 to 3 oz. (60–85 ml.) of mucopurulent sputum daily, a culture from which yielded pneumococci. She was treated with antibiotic and routine antispasmodic drugs, and, concurrent with the clearing of the pus from the sputum, she greatly improved. Two days later, however, in spite of continued penicillin and the fact that her sputum remained mucoid, she relapsed severely, with a return of severe wheezing. She started hydrocortisone inhalations in a dose of one capsule three times a day and made steady improvement, becoming almost symptom-free at the end of a week. She continued on daily inhalations, the dose varying between one and two capsules daily, and remained greatly improved for 18 months up to the time of writing, although with considerable day-to-day variation. She continued to need antispasmodic drugs, but no further antibiotic treatment has been necessary.

Assessment of Proportions of "Inhaled" Powder Entering the Stomach and Tracheo-bronchial Tree

It seemed certain that some of the "inhaled" powder would be swallowed whatever method of inhalation was used, since some would become arrested in the mouth, pharynx, and glottis.

An attempt was made to estimate, roughly, the relative proportions of powder entering the stomach and the tracheo-bronchial tree in two normal subjects who "inhaled" fine powder, propyliodine ("dionosil"), in exactly the same manner as used for the hydrocortisone. It was hoped that a partial bronchogram might be obtained in this way, but, in spite of the fact that 4 to 5 g. of the powder was "inhaled," subsequent chest *x*-ray pictures showed only a few small opacities in the bronchial tree, probably due to clumping of the powder. It could be seen, however, that there was a considerable quantity of the opaque medium in the stomach of both subjects. This experiment was therefore repeated at a later date. Ryle tubes were passed and the stomach's contents aspirated, and the quantity of propyliodone present was estimated. It was found that about half the "inhaled" powder was present in the stomach in each case.

Although this powder was finely ground, the experiment was hardly comparable to the hydrocortisone lactose inhalations because the propyliodone was far more irritating, and necessitated considerable local anaesthetization of the throat and larynx before it could be "inhaled" at all. In addition there was a greater tendency for the powder to form "clumps." In view of these facts, three normal subjects each "inhaled" 1 g. of finely powdered lactose, having already swallowed a Ryle tube, and after drinking 4 oz. (114 ml.) of water the stomach contents were aspirated as thoroughly as possible. It was found that about 20% of the total powder "inhaled" had entered the stomach of each subject. This lower proportion was expected in view of the comparative ease of inhalation of the lactose powder as compared with propyliodone.

Discussion of Results

The early results of treatment were remarkably good and many patients obtained rapid relief of wheezing, often within a few hours and after days of unsuccessful preliminary routine treatment. Once relief had been achieved, it was unusual for further acute attacks to occur for a time, provided the inhalations were continued. In the groups with chronic asthma, however (groups 2 and 4) and the group with recurrent acute asthma and intermittent infection (group 3), relapses began to occur after the first month, and became more frequent the longer the follow-up continued. These relapses were not necessarily complete, however, and some of the patients classified as having relapsed were confident that they remained better than before starting the inhalations. On the other hand, some of the patients regarded as having maintained their improvement up to the time of writing were certainly not so well at the time of assessment as they had been earlier in their treatment.

It is clear that in these groups of patients there is a tendency to relapse if treatment is maintained in the same way as was shown to occur in the Medical Research Council's (1956) trial in chronic asthma, where the advantage of patients receiving cortisone by mouth over those receiving placebo tablets rapidly diminished after the first two months until at the end of six months there was no significant difference between the two groups. In the group with recurrent acute asthma without infection, however, the

improvement has been maintained in all but one patient over a mean period of 10 months. All these patients have been able to stop the inhalations as soon as relief of the bouts of wheezing has been obtained and to restart at the onset of the next attack, whereas the patients with chronic asthma usually found it impossible to stop the inhalations without rapid return of wheezing, although they were able to vary the daily dose according to their symptoms.

The results were very disappointing in the patients with wheezy bronchitis (group 5), and only three out of nine improved, and the disability in these three was relatively mild. This result is not surprising, since we have found, in agreement with Moyes and Kershaw (1957), that little or no benefit is obtained in patients with chronic wheezy bronchitis and infection by the addition of oral corticosteroid drugs to long-term antibiotic therapy. It would also seem that the presence of considerable secretion in the bronchial tree is against successful local action of hydrocortisone. We have, however, treated a few very early cases, in which cough, sputum, and wheezing have been present for only a few weeks or months, with combined antibiotics and hydrocortisone inhalations with encouraging results, and it seems possible that at this stage local hydrocortisone may help in the resolution of the hypersensitive and irritable state of the bronchial mucous membrane during and after infection.

Reason for Relapse.—The reason for relapse in some of our patients who did well for a time is uncertain. It is possible that local tolerance to the hydrocortisone in the bronchial mucous membrane develops, but it would certainly not appear to be due to the development of a general tolerance to the corticosteroid group of drugs, as nine of these patients, after relapse, responded very well to the addition of a relatively small dose of oral prednisone (5 to 10 mg. daily) while continuing with hydrocortisone inhalations. One of these patients developed a gastric ulcer while taking prednisone, and, after a period of hydrocortisone inhalations only, oral cortisone (25 mg. daily) was added with maintained benefit and absence of gastric upset.

Local or General Action

Cotes *et al.* (1956) showed that there was a rise in urinary excretion of 17-hydroxycorticosteroids after the inhalation of fine particle hydrocortisone powder. This demonstrated that some general absorption had taken place, but the site of the absorption was uncertain. From our observations there would seem to be little doubt that a considerable proportion of the inhaled powder enters the stomach and is absorbed. This proportion probably varies greatly according to the condition of the patient and the technique followed by him, but is probably in the region of 20–50%. Most of the remainder must enter the tracheo-bronchial tree, and the depth of penetration probably also depends on the preceding factors. It would seem a fair assumption that some of this powder will be absorbed from the bronchial mucous membrane, and highly probable that some will be expelled by cough and cilia action and finally swallowed and absorbed from the stomach. If the dosage is large, therefore, there must be some general action from absorption of the hydrocortisone, and doubt may arise about whether or not any local action occurs.

Assuming that about 75% of the "inhaled" powder is absorbed, we can perhaps compare the results of the inhalations of hydrocortisone with those likely to be obtained by the same dose of oral cortisone, since oral hydrocortisone is recognized to be somewhat more powerful than cortisone: the starting dosages in the M.R.C. trials in chronic asthma and status asthmaticus were 300 and 350 mg. of cortisone daily respectively, and on the seventh day patients in the chronic asthma group were still receiving 100 mg. of cortisone daily, the dosage after this being left to the physician in charge of the patient. Foulds *et al.* (1955) gave 15 mg. of hydrocortisone acetate powder by inhalation daily and had good results in 12 out of 15 patients. Our starting dosage scheme was varied according to the patient's condition and the technique followed by him, but the maximum was 45 mg. daily for the first week, and the maximum maintenance dose was 30 mg. daily, the usual maintenance dose being 15 mg. daily.

The early results in our series were good in most patients, and often remarkably rapid, with relief of previously intractable wheezing within a few hours in some. We doubt whether similar results would have been obtained with a starting dose of 15 to 45 mg. of oral cortisone daily. We therefore believe that in successfully treated patients a considerable local action takes place. Further strong confirmation of this was obtained by Brockbank and Pengelly (1958), who report good results in a controlled trial using a much lower dosage of hydrocortisone powder than in the present investigation.

Indications for Hydrocortisone Inhalations

It would appear that hydrocortisone powder inhalations have most chance of maintained beneficial effect in patients with recurrent acute asthma with symptom-free intervals. In these cases the treatment can be used to break the individual attack and then be stopped, thereby reducing the chance of loss of the local effect of the powder. The results in chronic asthma are clearly not so good, for, although most of these patients improved with the inhalations for a time, relapse was more frequent, and in advanced cases the improvement did not appear to be as great as may occur with oral prednisone. However, the treatment is relatively cheap and certainly far less likely to produce severe complications; it would therefore seem well worth while trying as a first measure, since relapse does not seem in any way to jeopardize the chances of success with oral prednisone.

In patients with intermittent infective bouts followed by acute asthma, very good results can often be obtained by hydrocortisone inhalations in combination with antibiotic treatment.

Nine of our patients were seriously ill and could be classed as being in status asthmaticus at the onset of treatment, and only two failed to respond; but we feel that the ability to inhale the powder is so restricted while the extreme wheezing continues that it is probably preferable and safer to use intravenous hydrocortisone and aminophylline, or oral cortisone, or prednisone in such severely ill patients, at least until some partial relief has been obtained, when treatment could be continued with hydrocortisone inhalations with or without combined oral treatment. The two patients who failed to respond were obese middle-aged women with marked wheezing and extremely poor respiratory movements.

This treatment is unlikely to be effective in patients with advanced wheezy bronchitis, but is probably worthy of trial in combination with antibiotics in patients with symptoms of mild bronchitis which have been present for only a few weeks or months.

Summary

53 patients with asthma or bronchitis were treated for periods of two months to two years with inhalations of fine-particle hydrocortisone acetate powder.

These inhalations were found to be an effective form of treatment in many patients with bronchial asthma. There is a strong tendency to relapse if the treatment has to be maintained, but prolonged benefit may continue if the inhalations can be used intermittently for recurrent attacks of asthma.

Although this treatment may be successful in status asthmaticus, it is probably less effective in this condition than intravenous or oral corticosteroid drugs, and its use is not recommended if the patient is dangerously ill.

A considerable proportion of the "inhaled" hydrocortisone is probably absorbed, but the dosage is low compared with that used in oral corticosteroid therapy.

and the chance of toxic effect is therefore much less. The optimum dosage is uncertain, but it probably varies from patient to patient.

Little or no benefit is likely to be obtained from this form of treatment in patients with established chronic bronchitis.

We are indebted to the late Dr. W. J. Dunn, Dr. J. Shafar, and many other doctors for their co-operation; to Dr. G. Behr and Mr. H. Lawrie for carrying out the biochemical estimations; to Dr. J. Edge for helpful criticism; to Mr. E. Tallett, the hospital group pharmacist, for his enthusiastic co-operation throughout; to Mrs. J. Withnell for the secretarial work; to Messrs. Upjohn of England Ltd., who provided the material used in the early part of the series; and finally to Messrs. Paine & Byrne Ltd., who provided the pabracort inhalers and material used by most of the patients.

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INHALATION OF HYDROCORTISONE ACETATE FOR BRONCHIAL ASTHMA

A SHORT-TERM CONTROLLED TRIAL

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The beneficial effects of oral cortisone in some asthmatic patients have been clearly demonstrated by the Medical Research Council (1956). Hydrocortisone, when given locally as a surface application on the skin or by injection into the joints and tendon sheaths, is of value in many allergic and inflammatory conditions, and when inhaled into the nose as a powder may considerably improve allergic conditions of the nasal mucous membrane, including hay-fever (Foulds *et al.*, 1955); Herxheimer and McAllen, 1956). It would therefore seem reasonable to expect a favourable response in allergic bronchial asthma if, by inhalation, sufficient hydrocortisone could be brought into contact with the surface of the bronchial mucous membrane.

Foulds *et al.* (1955) used hydrocortisone acetate in fine-particle powder for 15 patients with bronchial asthma, with encouraging results in 12. Brockbank *et al.* (1956) found no evidence of benefit in patients treated with inhalations of hydrocortisone succinate solution in a "blind" controlled trial; but in a similar trial, using hydrocortisone acetate powder inhalations, Brockbank and Pengelly (1958) report improvement in a statistically significant number of patients on the hydrocortisone as compared with a placebo powder.

The assessment of benefit from any form of "new" treatment in bronchial asthma is notoriously difficult, since so many factors, including emotion, may be important in precipitating attacks and prolonged natural remissions may occur. It is therefore desirable to submit any method of treatment to a controlled trial before a fair assessment of its value can be made.

The purpose of the present investigation is to test by a controlled trial the short-term effect of the inhalation of hydrocortisone acetate in fine-particle powder in cases of bronchial asthma.

Material and Method

The patients selected for the trial had been subject to bronchial asthma for at least one year, and with one exception the condition had been severe enough to necessitate periods off work. The exception was a patient whose attacks were almost entirely nocturnal. In no instance was the history or the state of the sputum indicative of the presence of considerable recurrent or chronic bronchial infection. Patients who had more than ½ oz. (7 ml.) of mucoid sputum daily or who had had any previous treatment with corticosteroid preparations or corticotrophin were excluded.

The "double blind" method of trial was used and patients regarded as suitable were placed by random selection by the hospital group pharmacist into either the hydrocortisone or the placebo group. Both groups were treated by the inhalation of powder from capsules with the aid of a "pabracort" inhaler. The capsules contained either 15 mg. of hydrocortisone acetate (ground to a main particle size of 5 microns), together with 75 mg. of lactose or, in the case of the placebo, 100 mg. of lactose, also in fine particle powder. It was not felt necessary to adopt a rigid dosage scheme, since previous experience with this treatment had suggested that the number of capsules used each day probably bore no close relationship to the quantity of powder reaching the bronchial mucous membrane, and that this depended to a considerable extent on the intelligence of the patients and their ability to inspire deeply.

It was noted in this respect that no settled regime of dosage of oral cortisone was adopted in the Medical Research Council (1956) trial in chronic asthma after the first week of treatment.

The starting dose therefore varied between three capsules a day in severe cases that began the trial during an exacerbation, and one capsule a day taken as half a capsule twice daily in those beginning during a relatively mild phase. The maintenance dose was adjusted according to response, the maximum being two capsules daily and the minimum half a capsule daily. Most patients were maintained on one capsule daily. Patients were given any other routine treatment thought necessary, and where severe wheezing was present bronchial dilator drugs were used directly before the inhalation of the trial powder to facilitate deep inspiration.

In patients who remained severely ill and who had failed to improve on general treatment together with trial inhalations after several days, a "blind" change of treatment was made to the other half of the trial, the patient being unaware that any change had been made. In less severely ill patients who were progressing satisfactorily, but in whom the response was not very clear-cut, a "blind" change of trial treatment was made after one to two months.

Results

The assessment of the results of treatment was made both on subjective and on objective grounds. All patients had had prolonged routine treatment before starting the trial inhalation, and this provided a baseline from which the changes in signs and symptoms could be judged. All patients were seen by the same physician at monthly intervals or less while remaining on the trial. Special attention was paid to the symptoms of dyspnoea and tightness of the chest, to exercise tolerance, and to the need for bronchodilator drugs. On physical examination the presence or absence of wheeze was noted and, if present, was assessed as slight, moderate, or severe, on each visit. In patients with recurrent acute asthma, considerable reliance often had to be placed on the history concerning the frequency, length, and severity of the attacks before and during treatment, and a relatively longer period of observation was usually neces-

sary. The assessment of the result of treatment was made in each patient as soon as it was felt that there was adequate evidence one way or the other. The length of treatment before assessment varied between one week in two severely ill patients who had failed to respond, and whose trial treatment was therefore changed, and six months in a patient with recurrent acute asthma who continued to improve on placebo capsules. The mean period before assessment was six and a half weeks. In all patients whose trial treatment was changed, a separate assessment was made at the end of each individual trial period, and the trial remained "blind" until the second assessment had been made.

TABLE I

	Improved	Not Improved	Total
Hydrocortisone	19	4	23
Placebo	6	9	15
Total ..	25	13	38

The results of inhalation of hydrocortisone acetate powder and of placebo powder in 38 trial periods in 26 patients (14 men, 12 women) with bronchial asthma are shown in Table I. If the χ^2 test with Yates's correction for continuity is applied we get a value for χ^2 of 5.5, which is significant at the 2% level.

These results are perhaps open to the criticism that the treatment of 12 patients was changed from one part of the trial to the other, and that the effect of the first treatment might persist after the change had been made. The exclusion of the results of the second period in treatment in these 12 patients gives the figures shown in Table II. The value of χ^2 for these figures is 4.3, which is significant at the 5% level.

TABLE II.—*Results of Inhalation of Hydrocortisone Acetate Powder and of Placebo Powder in 26 Patients (14 Men, 12 Women)*

	Improved	Not Improved	Total
Hydrocortisone	14	3	17
Placebo	3	6	9
Total ..	17	9	26

Change of Trial Treatment

Twelve patients were changed "blindly" and without their knowledge from one-half of the trial to the other. Six of these changed from the placebo to the hydrocortisone powder; all had been no better on the placebo and one remained unchanged on the hydrocortisone; the other five made definite improvement on the hydrocortisone. Two of these patients had been very seriously ill despite energetic routine measures before the trial started and during the placebo inhalations, but both responded dramatically when changed to hydrocortisone after one week, and on the night the change was made both slept well for the first time for many days. Six patients were changed from hydrocortisone to placebo inhalations; three of these had improved on the hydrocortisone, but the asthma had been relatively mild and the change was made in order to obtain a more clear-cut result. One of these immediately relapsed on the placebo, but the other two maintained their improvement until the trial was terminated after two and three months respectively. Two patients were not improved on either half of the trial. One man, after an initial good response to hydrocortisone in hospital, relapsed on returning home and was therefore assessed as "not improved"; he was changed to the placebo powder, on which he has remained well until the time of writing, a period of two months.

Discussion

It is unfortunate that by chance 17 patients should have been allocated to the hydrocortisone and only nine to the placebo inhalations, but we feel there is little doubt that the inhalations have a beneficial effect for a time in some patients with bronchial asthma. The rapid improvement of five patients when changed from the placebo to the hydrocortisone was especially impressive. For success it is essential that enough powder should contact a wide surface area of bronchial mucous membrane. The powder is therefore ground fine in order to allow penetration to the small bronchioles.

Foulds *et al.* (1955) suggested that there was no advantage in the inhalation of more than 15 mg. of hydrocortisone daily. Although we have made no specific tests on these lines, the method of inhalation is so inexact, and the ability of the patients so variable in spite of careful training, that we feel this quantity may be insufficient in some patients, especially where in the initial stages of treatment chest movements are very poor and respiration is shallow owing to bronchial spasm. One of the four patients assessed as being no better on hydrocortisone, and another who improved slowly, were obese, middle-aged women with severe wheezing and distended chests who found it almost impossible to inspire deeply even with the help of preceding bronchial dilator drugs. We think that in this type of patient at least three capsules—that is, 45 mg. of hydrocortisone powder—should be inhaled daily at first to give a fair chance of success.

The disadvantage of the bigger dose is that the absorption will be higher and toxic effects more likely, and doubt may arise whether any benefit is due to local or general effects. In successfully treated patients, however, the dose can be reduced to one capsule daily (15 mg.) within a few days, and it would seem unlikely that this dosage would produce sufficient general absorption to have significant side-effects or influence on the asthma. There were no complications in the present series.

Summary and Conclusion

A short-term "blind" controlled trial of inhalations of hydrocortisone acetate in fine-particle powder has been carried out in 38 periods of treatment in 26 patients. The number of patients improved in the hydrocortisone group as compared with the placebo group was at a statistically significant level.

It is therefore concluded that hydrocortisone acetate powder inhalations are an effective form of short-term treatment in some patients with bronchial asthma.

We are indebted to the late Dr. W. J. Dunn, Dr. J. Shafar, and the many other doctors for their co-operation; to Dr. J. Edge for helpful criticism; to Dr. E. Tallett, the hospital group pharmacist, for his enthusiastic co-operation throughout; to Mrs. J. Withnell for the secretarial work; and to Messrs. Paines & Byrne Ltd. for providing the "pabracort" inhaler, and the material for the trial.

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The Care of the Elderly is the report of the Ninth Conference of the National Old People's Welfare Council. This was held on April 17 and 18, 1958, in London. The conference included discussions on the future pattern of care for the elderly through health and welfare services (opening speaker, Mr. Derek Walker-Smith, Minister of Health); preparation for retirement (opening speaker, Mr. W. A. Sanderson); the housing of the elderly (opening speaker, Mr. J. R. Bevins, parliamentary secretary to the Ministry of Housing and Local Government); recruitment and training of workers among the elderly; problems of communal homes; visiting; surveys and research; and the changing pattern of comprehensive care (opening speaker, Professor R. E. Tunbridge). This report is obtainable from the National Old People's Welfare Council, 26, Bedford Square, London, W.C.1, price 3s. 6d., quoting ref. no. 534.

FOETAL CELLS IN THE MATERNAL CIRCULATION DURING PREGNANCY

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Levine, Katzin, and Burnham's (1941) brilliant exposition of maternal iso-immunization during pregnancy as the cause of haemolytic disease of the newborn has been vindicated in thousands of cases. Direct proof that this iso-immunization was due to an antigenic stimulus from the foetus was produced by Chown's (1954) investigation, which demonstrated foetal cells in the maternal circulation. A further paper on this subject was published by Dunsford (1957), who also found foetal cells amongst the maternal cells. In both cases the foetal cells were discovered in a blood specimen obtained after the birth of the baby. Chown's patient developed, after the usual latent period, an anti-rhesus antibody, thus making the picture complete. Bromberg, Salzberger, and Abrahamov (1956) succeeded in demonstrating foetal haemoglobin in the maternal circulation during some pregnancies, and as this could be shown not to be a normal occurrence it was also very suggestive of a "leak" in the placenta.

Case Report

A married woman aged 32 had an abortion at three months in 1953 and expected her first baby in June, 1955. Her blood group was determined on two occasions during this pregnancy as group A, rhesus negative. The serum gave no evidence of the presence of any abnormal antibodies. The baby was stillborn, but no cause for this stillbirth was found.

The patient became pregnant again in 1957, but her dates were quite uncertain; she thought that her E.D.D. was approximately mid-February, 1958, but when she attended for her first antenatal investigation on January 5, 1958, this did not seem to correspond to the clinical findings. A blood specimen gave both unexpected and unusual findings. The specimen grouped both by cell and by serum grouping as group A. However, when the cells were investigated for their rhesus group, an anti-C plus anti-D and an anti-D testing serum produced some agglutination, which to the technician seemed to be a result conflicting with our previous findings. A full investigation was therefore carried out, and this showed that both anti-C and anti-D sera produced small agglutinates "in a sea of unagglutinated cells," the typical picture of a "mixed field." Anti-E gave a negative result and anti-c almost complete agglutination. (All sera used were saline agglutinating "genotype" sera.) This investigation was repeated twice on cells from the same specimen and identical results were obtained. At the same time an investigation of the serum gave definite evidence of the presence of a low-titred blocking anti-rhesus antibody of anti-D specificity.

The presence of D-positive cells together with an anti-rhesus antibody caused us to investigate the cells for "coating," and the direct Coombs test was in fact found to be quite strongly positive, though again a "mixed field" was noted. The specimen which had given these results was a small specimen of clotted blood, and to prepare an eluate the clot was passed through an ordinary tea sieve. The cells thus obtained were thoroughly washed and an eluate was prepared from them by the method previously described (Weiner, 1957). The eluate had typical anti-D activity when tested by means of the indirect Coombs test.

The patient was immediately written for and a further specimen was obtained (approximately eight days after the specimen described above). This further specimen, however, showed no trace of any D-positive cells in spite of the exhibition of very strong antisera. All cells were found to be rhesus negative (cde/cde). Also an indirect Coombs test with very strong blocking anti-D gave a negative result. The titre of the anti-rhesus antibody in the serum had, however, increased considerably in the meantime.

A specimen from the husband was found to be group O, rhesus positive, phenotype CcDEe (most likely genotype CDe/cDE).

From the results obtained it was concluded that the agglutinated cells in the first specimen had been derived from the baby and that these cells had been coated by a preformed maternal antibody. From the results obtained one could even predict the genotype of the baby as CDe/cde, though it was not possible to say anything about the baby's ABO group.

It was thought inadvisable to allow the pregnancy to go to full term, and a caesarean section was performed on February 8, when clinically it was thought that she was not at term. The baby's blood group was found to be A (identical with the mother's group) and to have the predicted genotype CDe/cde. The direct Coombs test was very strongly positive. Bilirubin was 7.9 mg. per 100 ml., but the haemoglobin was found at the very low level of 5.1 g. per 100 ml. The baby, a girl, weighed 6 lb. 11 oz. (3.04 kg.). Her clinical condition was very poor from the moment of birth. She was pale, grey, and oedematous. She was kept in continuous oxygen, and nikethamide was injected into the umbilical vein. An exchange transfusion was started as soon as possible. Although the exchange was smooth, it was stopped after about 65 ml. of blood had been exchanged per pound (143 ml. per kg.) body weight, because of the extremely bad condition of the baby. It was intended to repeat the procedure if her condition should show even a slight improvement after this initial exchange. However, the condition deteriorated still further, and the baby died approximately 15 hours after birth.

At necropsy a small tentorial tear, together with a large cerebral haemorrhage around the cerebellum and the base of the brain, was found. There were no effusions, the lungs were atelectatic and showed petechial haemorrhages. The liver and spleen showed the typical changes of haemolytic disease of the newborn with very active extramedullary haematopoiesis.

Discussion

Previous authors have reported foetal cells in the maternal circulation after the birth of the baby. These cells might, of course, have entered the maternal circulation during delivery, and the finding of these cells in the maternal circulation was most suggestive but not absolute proof of the presence of foetal cells in the maternal circulation during the pregnancy. We could demonstrate these cells, however, during the pregnancy and even describe their genetic make-up.

The exact date when the mother developed the anti-rhesus antibody is not known, and it is, of course, possible that it had developed after the second pregnancy—that is, before this baby was conceived. The antigenic stimulus could have been provided by the stillborn baby in 1955, similar to the cases described previously (Weiner and Hallum, 1950). We did not attempt to estimate the amount of foetal blood which had been "transfused" into the mother, as we were aware of the simultaneous presence of the maternal antibody

against them, making a quantitative assessment quite unreliable. The baby must, however, have bled extensively, as the extremely low level of haemoglobin (5.1 g. per 100 ml.) is unlikely to have been produced by haemolysis only. It seems much more likely that this low level was the result of blood loss plus haemolysis. The production of anaemia in babies through blood loss into the maternal circulation had been suggested by Wiener (1948), and we think that this case is a further example, though no doubt haemolysis played some part in the production of the anaemia.

Summary

A case of foetal blood loss into the maternal circulation is described. The foetal cells were recognized during the pregnancy in the blood stream of an immunized mother.

The maternal serum contained an anti-rhesus antibody which coated the foetal cells in the maternal circulation and gave rise to a positive direct Coombs test. It was successfully eluted from the coated cells.

We thank Mrs. June Wingham for much technical assistance.

ADDENDUM.—Since this paper was submitted a further article on transplacental bleeding from the foetus (Goodall *et al.*, 1958) has appeared.

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INTRAVENOUS PHENTOLAMINE FOR PHAEOCHROMOCYTOMA AND "ADRENALINE SHOCK"

BY

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The management of the usual patient with phaeochromocytoma is now well established, with a welcome improvement in mortality (Kvale *et al.*, 1957). The most significant factor in this success has probably been the use of oral or intramuscular phentolamine ("rogitine"*) to block the effects of circulating adrenaline and noradrenaline (Iseri *et al.*, 1951; Emlet *et al.*, 1951; Newton *et al.*, 1955).

We wish to focus attention on the management of the unusual patient with phaeochromocytoma in whom the classic symptomatology of the disease is punctuated by wild unpredictable fluctuations of the systemic blood pressure with periods of alarming hypertension alternating with periods of profound shock. Such a patient has recently been under our observation, and in this instance the usual doses of phentolamine intramuscularly were found to be ineffective; however, a continuous intravenous phentolamine infusion produced dramatic improvement and, we believe, was life-saving. It enabled us effectively and leisurely to organize a programme of therapy for the operative and post-operative periods.

*Known as "regitine" in the U.S.A.

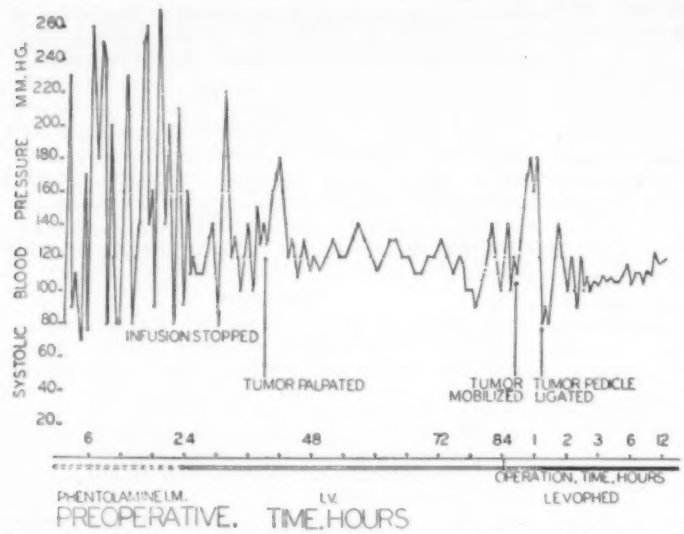
Case Record

The patient, an 18-year-old coloured girl, was first seen at the Cook County Hospital on January 8, 1957. She complained of nervousness, sweating, difficulty in breathing, severe lower abdominal pain, and vomiting of four hours' duration. For one year prior to admission she had had daily episodes of sweating and nervousness which began on arising and persisted until noon. Upon inspection she was seen to be orthopnoeic, grey, cold, and perspiring. The oral temperature was 101° F. (38.3° C.). The blood pressure was 80/0. The pulse was barely perceptible, with a rate of 140. The cardiac rhythm was regular. The left heart border was 3 cm. left of the mid-clavicular line in the fifth interspace. The heart tones were not unusual. Auscultation of the lungs disclosed fine and coarse moist rales throughout both lung fields. Upon palpation of the abdomen, a rounded mass, approximately 3 cm. in diameter, was detected in the left upper quadrant; it was in close proximity to the left kidney. The remainder of the physical examination showed nothing of importance.

Following palpation of the left upper quadrant of the abdomen, the patient began to tremble, her dyspnoea increased, and she sat bolt upright. She complained of a "nervousness," first in her abdomen and then "all over." This sensation was followed by increasing abdominal pain. The blood pressure was recorded as 230/17. The symptomatology suggested the presence of phaeochromocytoma complicated by acute left ventricular failure. Immediate therapy directed towards the relief of the left ventricular failure was successful. Additional therapeutic measures included sedation, complete bed rest, and elimination of all procedures which might augment tumour secretion. The patient's condition remained grave. Hypertensive–hypotensive swings in the systemic pressure continued, despite the administration of phentolamine intramuscularly in amounts of 5 mg. every four hours. For a period of 24 hours the blood pressure fluctuated between 290/140 and 80/0.

One of us (R. B. T.) suggested that phentolamine be given by continuous intravenous infusion. A solution of 30 mg. of phentolamine in a litre of 10% dextrose and water was infused intravenously at a rate of 20–80 drops a minute, depending upon the systemic blood pressure. The response was dramatic. The patient's sweating, pallor, coldness, and weakness disappeared, and within two hours she complained of hunger and was able to eat with obvious pleasure.

After surgical consultation, all agreed that the patient should be explored, but in view of her response to intravenous phentolamine there seemed to be no reason for hasty action. Two and a half days were allowed to elapse before the condition of the patient was considered to permit laparotomy. We were thus able to alert all personnel who were to be concerned with her care; and detailed check lists were prepared of all the procedures and medications necessary for proper management during and following surgery. During the 60 hours prior to surgery the patient received 250 mg. of phentolamine, and the blood pressure and pulse were recorded approximately every half-hour. Adjustments in the rate of flow of the infusion served to control all signs of tumour secretion. The patient had no symptoms, and there were no further hypertensive–hypotensive swings in the blood pressure (see Chart).



The systolic blood pressures recorded during the pre-operative period demonstrate the effect of continuous intravenous infusion of phentolamine. Also shown are the moderate blood-pressure excursions encountered during removal of the phaeochromocytoma.

Surgical premedication was by scopolamine and meperidine (pethidine) hydrochloride. The method chosen was thiopentone sodium for induction, followed by maintenance of anaesthesia with nitrous oxide through an endotracheal airway (Zintel and Bottie, 1956). Muscular relaxation was provided by an intravenous drip of suxamethonium. During induction of anaesthesia and throughout the operative period the systolic blood pressure was utilized to regulate the phentolamine infusion (30 mg. per 1,000 ml. of 5% dextrose and water). The abdomen was explored through a horizontal upper abdominal incision, and a phaeochromocytoma was found medial to the lower pole of the left kidney. The phentolamine infusion effectively controlled all hypertensive swings of the blood pressure during the period of anaesthesia induction and tumour manipulation. When the pedicle of the tumour was ligated the systolic blood pressure fell precipitously and was unobtainable for two minutes. An intravenous infusion of L-noradrenaline was started immediately (16 mg. per 1,000 ml. of 5% dextrose and water), and the hypotension was effectively controlled. L-Noradrenaline infusion in progressively decreasing amounts was continued for 12 hours post-operatively. The post-operative course was otherwise uneventful.

Discussion

Although there is ample experience to which one may refer for information concerning the management of the usual patient with phaeochromocytoma, there are few (Wilkins *et al.*, 1950; Rothermich, 1952; Gjøl *et al.*, 1957) which discuss the management of the patient in whom periods of alarming hypertension alternate with periods of profound shock. These wild swings in the systemic blood pressure are best explained if we assume that the rate of liberation of pressor substances from the tumour is inconstant. The truth of this assumption is supported by the observation that manipulation of the tumour through the abdominal wall would produce a dramatic hypertensive episode; we need not infer, however, that secretion ceases during the hypotensive episodes. Freeman *et al.* (1941) produced shock in unanaesthetized dogs by the continuous infusion of adrenaline, and the reports of Green *et al.* (1948) and Blacket *et al.* (1950) demonstrated that prolonged infusion of pressor amines was followed both in the experimental animal and in man by a period of hypotension. It is logical to assume that the infusion of pressor amines invokes compensatory mechanisms which favour hypotension if the infusion is terminated or if the rate of infusion is abruptly diminished.

In this instance, since intermittent intramuscular phentolamine failed to control the fluctuating blood pressure, we decided to administer the drug by continuous infusion. Not only were the hypertensive episodes immediately and completely controlled, and further hypotensive crises prevented, but the patient's general clinical condition was rapidly and markedly improved. We believe that the dramatic response of the patient is a reflection of the efficacy of this approach. Many patients with phaeochromocytoma are poor surgical risks. Our results in this case suggest that the prolonged pre-operative intravenous infusion of phentolamine may be of value in the preparation of these doubtful-risk patients, whether hypertensive-hypotensive crises are present or not.

Summary

A patient with a phaeochromocytoma, in whom the classic symptomatology was complicated by wildly fluctuating blood pressure, was managed by a continuous pre-operative intravenous infusion of phentolamine over a period of two and a half days with dramatic results. The tumour was removed by surgical excision and the patient's recovery was uneventful.

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The Wellcome Trustees have made a grant to the Medical Research Council of up to £26,000 for the provision of a vessel which could serve as a floating laboratory and means of transport for use by the Council's laboratories in the Gambia. On September 26 the *Lady Dale*, as the launch is named, was inspected at the boat yard of Aldous Successors Ltd., Brightlingsea, by a party from the Medical Research Council and the Wellcome Trustees. The *Lady Dale* will be based on Bathurst, at the mouth of the River Gambia, and will sail from there not only to the subsidiary field laboratories at Keneba, some 70 miles up-river, but also to other parts of the territory along the river where laboratory facilities would not otherwise be available. The research programme of the M.R.C. laboratories is concerned mainly with parasitic diseases, primarily malaria; in addition, the facilities of the laboratories, including accommodation, can be made available to visiting scientists. Formed originally after the second world war as a subsidiary of the council's human nutrition research unit in London, the laboratories are now an independent unit under the direction of Dr. I. A. McGREGOR.

PUERPERAL MENTAL ILLNESS

A FOLLOW-UP STUDY OF 75 CASES

BY

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Mental illness occurring after childbirth is a common condition. The incidence in all confinements has been variously estimated as 1 in 400 (Boyd, 1942) to 1 in 1,200 (Morton, 1934). It is the cause of 2 to 8% of female admissions to mental hospitals all over the world (Smalldon, 1940; Boyd, 1942; Brew and Seidenberg, 1950). What is the prognosis for recovery in the individual case? What is the likelihood of recurrence should the patient become pregnant again? Can recurrence be prevented by social, medical, or psychiatric prophylactic measures? Is termination of pregnancy indicated in any cases, and should sterilization ever be considered? This study is an attempt to answer these and other questions in the light of experience at St. Patrick's Hospital.

Material and Methods

This investigation is a study of 75 patients suffering from puerperal mental illness who were admitted to St. Patrick's Hospital, a private psychiatric hospital, between January, 1947, and June, 1957. During the 10½-year period 80 cases were admitted (2% of 4,006 female admissions) of which five could not be traced. The age of the patients ranged from 21 to 45, with an average of 31.5 years. Patients, or their relatives, were required to fill in a questionary giving details about their present state of health, information about all pregnancies, and the occurrence of nervous symptoms, whether associated with childbirth or not. Further correspondence and telephone calls were made in over three-quarters of the cases to elicit details from the patient and to gain objective information from the husband or family doctor. All patients were invited to attend hospital for interview, but, as they came from all over Ireland and the follow-up period was long, a good response could not be expected. The sources of information are shown in Table I.

TABLE I.—*Sources of Information*

Patient	Questionary alone	22		41
	,, plus letter	19		
	Personal interview			18
Husband	Questionary alone	11		29
	,, plus letter	18		
	Personal interview			3
Family doctor				41
Sole information from patient's questionary				4
Information from personal interview or family doctor				55
,, ,, husband				14
Total				73*

* 2 patients had died.

In only four instances (three cases of depression and one of schizophrenia) was there no objective information about the patient's present state of health. The patients interviewed were not selected in any way, but tended to come from the Dublin area (13 of 18).

Time of Onset

In this survey all illnesses which began within six months of childbirth were included as puerperal. Some investigators in the past have taken the obstetrical puerperium of six weeks as their standard, later illnesses being termed lactational. There seems to be no advantage in this. The time of onset of symptoms is shown in Table II. In 14.7% of cases the earliest symptoms were noticed during pregnancy, but there was a clear-cut exacerbation of symptoms after confinement, necessitating admission to hospital. It must be noted that in some cases the onset of symptoms was gradual and difficult to date accurately. In many, however, it was dramatically sudden. In 60% of the cases the first symptoms were noticed within one month of delivery.

TABLE II.—*Distribution of 75 Cases According to Time of Onset of Symptoms*

During pregnancy	11 (14·7%)
0–14 days after birth	33 (44·0%)
14–28 ,, ,, ,,	12 (16·0%)
28 days–6 months after birth	19 (25·3%)

These figures correspond closely to an average of several series reviewed by Boyd. Mental illness precipitated by abortion has been excluded from this series.

Type of Illness

The cases fell into five diagnostic groups, as follows:

1. *Affective Psychosis.*—This was defined as an illness in which there is a greatly exaggerated emotional response, either depression or elation. Delusions may be present, but they are in keeping with the emotional change—for example, self-accusation or ideas of unworthiness in association with depression. Early wakening and morning exacerbation of depression are often present.

2. *Schizophrenia.*—There is distorted thinking on personal topics, which are often projected as delusions or hallucinations without a corresponding emotional display (Skottowe, 1942). The affect may be one of apathy or fear, or there is incongruity of affect.

3. *Schizoaffective Psychosis.*—There is definite evidence of distorted thinking, delusions, and hallucinations characteristic of schizophrenia. In addition, there is a well-marked affective element, usually depressive with ideas of guilt, but sometimes maniacal. This corresponds to a group called "mixed schizophrenia" by Hemphill (1952).

4. *Toxic Confusional State.*—This was diagnosed only when two conditions were fulfilled: firstly, there was definite evidence of physical illness, such as infection of the genital tract, or breast; secondly, there was confusion, disorientation in time and place, faulty perception, amnesia, and often vivid auditory or visual hallucinations.

5. *Hysteria.*

The distribution of cases is shown in Table III.

TABLE III.—*Distribution of 75 Cases Acording to Diagnosis*

Diagnostic Group			Total
Affective psychosis:			
Depression	27		28 (37·3%)
Mania	1		
Schizophrenia			15 (20·0%)
Schizoaffective psychosis:			
Depression	24		29 (38·6%)
Elation	5		
Toxic confusional psychosis			2 (2·6%)
Hysteria			1 (1·3%)

The lack of standardization of psychiatric terminology, and the fact that many authors do not define their diagnostic criteria, make comparison with other series very difficult. For instance, the incidence of schizophrenia varies from 20 to 58% in reported series. The incidence of toxic confusional states has fallen over the years, owing partly to improved obstetrics and the advent of antibiotics, and partly to altered diagnosis. Cases previously called "non-toxic delirium," as described by Boyd, would now be classified as schizophrenia. Foundeur *et al.* (1957) found no cases of toxic confusional state in their series of 100 patients, though, unlike other observers, they had a high incidence (21%) of psychoneuroses. The experience in this country is that neurotic reactions, though common, rarely necessitate admission to hospital.

Treatment, Results, and Follow-up

The time interval between discharge and follow-up is shown in Table IV.

TABLE IV.—*Time Interval Between Discharge and Follow-up*

Diagnostic Group	4 Months–2 Years	2–4 Years	4–6 Years	6–11 Years	Total
Affective	11	8	3	6	28
Schizoaffective	3	9	5	10	27
Schizophrenic	4	3	3	5	15
Toxic confusional	1	0	1	0	2
Hysteria	0	0	0	1	1
Total	19	20	12	22	73*

* 2 patients died.

Affective Group

In this group (27 with depression and 1 with mania) electroplexy was the standard treatment. The immediate response was good in all cases. The average number of treatments given was 7.4, and the average stay in hospital was 5.5 weeks. Of the 28 patients 13 recovered with one course of electroplexy (four to nine treatments)—that is, they had lost all psychotic symptoms and their pre-psychotic personality was restored. Ten cases (including the patient with mania) relapsed within 17 days of ending the first course, but recovered after a second course. Four patients required maintenance treatments, but had all recovered within 4½ months of admission to hospital. One patient who relapsed four weeks after a satisfactory response to a course of treatment refused to return to hospital, and was still depressed five months after the onset of her illness.

Follow-up (average 2½ years after discharge) showed that 24 of the 27 were in normal health, although one had had a further puerperal depressive illness and three had had further non-puerperal illnesses, all of which responded well to electroplexy. Two patients complained of minor neurotic symptoms and one was undergoing treatment for a non-puerperal depression.

The immediate prognosis of affective disorders in the puerperium is therefore excellent and full recovery can be expected with electroplexy.

Schizoaffective Group

Of the 29 patients 28 were treated with electroplexy, and 15 of these had in addition insulin coma therapy (Sargant and Slater, 1954). The average stay in hospital was 12.8 weeks. One patient, who had severe diarrhoea, died suddenly on the fifth day after admission, probably from pulmonary embolism, but necropsy was not carried out. She had been treated with antibiotics and sedatives only. Of the 28, 18 were discharged as recovered and 10 as much improved. The latter had some residual symptoms and had not completely regained their pre-psychotic personality. However, they were considered fit to live at home and look after their family and house.

Follow-up (average 4½ years later) showed that 24 of the 28 patients were in normal health, although two had had further puerperal illnesses and one a non-puerperal psychosis, all of which again responded satisfactorily to treatment. Two patients complained of minor neurotic symptoms and one had died of pulmonary tuberculosis a year after discharge, no details of her mental state being obtainable. The remaining patient had never been completely well since the initial puerperal psychosis and had required admission to hospital for a further puerperal and non-puerperal illness. She was able, however, to live at home and look after her household.

In this group the standard initial treatment was electroplexy. If relapses occurred or if the schizophrenic element persisted when the affect was restored to normal, insulin coma therapy was given.

Schizophrenic Group

Of the 15 patients, 13 were treated with electroplexy, combined in nine cases with insulin coma therapy, in two with intensive reserpine therapy (Moore and Martin, 1957), and in one with chlorpromazine therapy. Of the remaining two patients, one was treated with reserpine therapy but later developed depression, which responded satisfactorily to electroplexy. The other had a spontaneous remission. The average stay in hospital was 12.4 weeks.

Six of the 15 patients were discharged as recovered and nine as much improved. Follow-up (average 4½ years later) showed that all 15 patients were in normal health. One patient had had a further puerperal psychosis, and one had had two further non-puerperal illnesses, all of which again responded to treatment.

These findings suggest that insulin coma therapy combined with electroplexy is a satisfactory treatment of puerperal schizophrenia. There is insufficient experience from this study to decide whether it can be replaced by tranquillizing drugs.

Toxic Confusional Group

Both the toxic patients were febrile and obviously ill—one with a septic parotitis, the other without clear cause—and both were markedly anaemic. They were treated with antibiotics, parenteral iron, vitamins, and sedatives. One recovered uneventfully and was discharged within six weeks. The other developed depressive symptoms when all signs of toxicity had cleared up: these responded to electroplexy and she was discharged as recovered 11½ weeks after admission. Follow-up showed that both these patients were in normal health.

Hysteria: Untraced Cases

The one case of hysteria had various treatments, including psychotherapy, carbon dioxide inhalations, modified insulin, and electroplexy. She was discharged as improved after 12 weeks. Follow-up showed that she remained as previously, a very neurotic personality, but had never required further treatment in hospital.

Of the untraced cases, two had affective disorders, two schizoaffective psychoses, and one schizophrenia. All five were discharged as recovered or much improved.

In all cases, irrespective of the diagnostic grouping, simple psychotherapy in the form of encouragement, explanation, and reassurance was given in addition to the physical methods of treatment. It was considered important, too, that all patients should join in the active occupational and social therapy routine of the hospital. In some cases iron and vitamin supplements were given. The sedatives used were mostly barbiturates.

Findings at Follow-up

The psychiatric state of the whole series at the time of writing (average follow-up period, four years) is shown in Table V.

Of the 75 patients 65 are now in normal health and two have died. Two patients only have residual psychotic symptoms and it is felt that the patient who is depressed should respond well to another course of electroplexy, if she would agree to come to hospital. Five patients have residual neurotic symptoms, three of these having always had neurotic personalities. One patient is having out-patient treatment for a mild non-puerperal depressive illness. The overall picture, therefore, is very good. It is worth noting that practically all the patients who were only thought to be much improved on discharge are now considered to be recovered. Not one of 75 patients has become a chronic hospital invalid.

TABLE V.—*Psychiatric State of the Whole Series*

Type of Illness	Died	In Normal Health	Residual Psychotic Symptoms	Residual Neurotic Symptoms	Undergoing Non-puerperal Psychosis	Total
Affective ..	—	24	1	2	1	28
Schizoaffective ..	2	24	1	2	—	29
Schizophrenic ..	—	15	—	—	—	15
Toxic confusional	—	2	—	—	—	2
Hysteria	—	—	—	1	—	1
Total ..	2	65	2	5	1	75

It has been stated that electroplexy should be avoided for one month after confinement because of the danger of embolism from the pelvic veins during the convulsion (Jacobs, 1943; Feldman *et al.*, 1946; Brew and Seidenberg, 1950; Hemphill, 1952). Feldman *et al.* reported a death eight hours after an E.C.T. in a woman, two months after delivery, who had thrombophlebitis of one leg. She probably had had a pulmonary embolus, but a necropsy was not carried out. This is the only case of embolism following E.C.T. given during the puerperium traced in the literature. In the present study 72 patients were given electroplexy, and 12 of these started a course within four

weeks of delivery. In one patient the course was started on the third post-partum day, in six patients on the 12th to 16th days, and in five on the 19th to 24th days. There was no case of pulmonary embolism. In all cases the convulsion was well controlled with the thiopentone and suxamethonium premedication. Impastato and Gabriel (1957) describe a series of 14 patients given controlled E.C.T. uneventfully within one month of confinement.

Incidence of Puerperal Psychoses in Other Pregnancies

The details of these psychoses are shown in Table VI and VII.

TABLE VI.—*Analysis of Other Puerperal Psychoses Related to Previous or Subsequent Pregnancies*

Type of Illness	No. of Patients who had other Pregnancies	No. of other Pregnancies	No. of other Puerperal Psychoses
Affective	22	71	9*
Schizoaffective	28	87	4
Schizophrenic	12	34	2
Toxic confusional	1	3	—
Hysteria	—	—	—
Total	63	195	15

* This figure includes 2 previous illnesses in one patient—the only one in the series who had more than 2 puerperal psychoses.

TABLE VII.—*Analysis of Pregnancies Subsequent to that Associated with the First Puerperal Psychosis*

	Patients	Puerperal Illness
1st puerperal illness	75	75
1st subsequent pregnancy	44	9 (20·5%)
2nd " "	23	3 (13·0%)
3rd " "	9	2 (22·2%)
4th " "	2	1
5th " "	1	—
6th " "	1	—
		15 (18·7%*)

* Calculated as a percentage of 80 total subsequent pregnancies.

It will be seen that 75 women had a total of 270 pregnancies with 90 associated puerperal psychoses—that is, for every pregnancy associated with a puerperal illness there were two normal pregnancies. After the first puerperal psychosis 1 in 5 (20.5%) of the patients had a recurrence with their next pregnancy. The overall relapse rate in all subsequent pregnancies was 18.7%.

Only six of the 11 patients who had had a non-puerperal psychosis prior to their first puerperal illness became pregnant again. They had a total of 12 subsequent pregnancies, three again becoming ill—one on two occasions. These three all fell into the affective group. The non-relapsers comprised two schizophrenics and one schizoaffective. These numbers are too small to conclude that having had a non-puerperal psychosis in addition to a puerperal one necessarily increases the risk in subsequent pregnancies.

It has been stated that it is wise for women who have had a puerperal psychosis to avoid becoming pregnant again for two or three years (Boyd, 1942 ; Parfitt, 1952). Our experience does not confirm this. 37 patients had another pregnancy after their illness in St. Patrick's Hospital, and 19 of them had their baby within two years, with two associated puerperal illnesses (10.5%). The remaining 18 had babies after the two-year period, with three associated puerperal illnesses (16.6%).

Some Aetiological Factors

Personality.—Information on this subject was not sufficient for the drawing of any definite conclusions. Neurotic features were much more frequently present in the schizoaffective and affective groups than in the schizophrenic. It was noteworthy, too, that 14 of the 15 schizophrenic patients showed no clear pre-psychotic schizoid features such as undue shyness, extreme sensitivity, or emotional coldness. This may have contributed to the excellent response to treatment in this group, for it is generally agreed that in any psychiatric illness the chances of recovery are higher if the personality is good.

Previous Mental Illness.—In 17 patients (22.6%) there was a past history of mental illness. The corresponding figure given by Hemphill (1952) was 13% and by Foundeur *et al.* (1957) 30%. The latter found that a matched control group of patients with non-puerperal psychoses had exactly the same incidence of previous mental illness.

Family History.—There was a 32% incidence of mental illness in near relatives (grandparents, parents, siblings, uncles, aunts, first cousins). This figure is of the same order as that obtained in patients with non-puerperal psychoses, but it is much higher than that for the general population. This strongly suggests that there is a genetic element in puerperal as in non-puerperal psychoses.

Physical Illness.—13 patients (17.3%) had some form of infection during the puerperium (breast abscess, 3 ; infection of the genital tract, 1 ; abscess of buttocks, 1 ; urinary infection, 1 ; septic parotitis, 1 ; phthisis, 1 ; pyrexia of unknown origin, 5). This cannot be compared directly with the published figures from maternity hospitals, as these are assessed on the basis of a rise in temperature to 100.4° F. (38° C.) or more within 14 days of childbirth. The morbidity figures from the Dublin Maternity Hospitals in the years 1953 to 1955 vary from 0.9% to 5.6%. The considerable disparity between these figures and 17.3% suggests that infection may have played some part in the causation or aggravation of puerperal psychoses. Twelve patients (16.0%) of this series had some degree of anaemia (haemoglobin less than 11.2 g. per 100 ml.). Gatenby and Lillie (1955) found that practically 24% of antenatal patients at the Rotunda Hospital, Dublin, had a haemoglobin of less than 10 g. per 100 ml. This would suggest that anaemia was of no aetiological importance in this series. Blood W.R. was positive in 2 of the 75 patients, without evidence of involvement of the central nervous system. There were two sets of twins in the series and four stillbirths. Eight patients (10.7%) had a prolonged labour or difficult birth. Seven had a caesarean section, at least three being performed on account of nervous symptoms.

Discussion

The findings in this study may be summarized as follows. Puerperal mental illness is not a psychiatric entity, the patterns of illness being the same as those in the non-puerperal state. The prognosis in puerperal illnesses—treated as outlined—is excellent, irrespective of the diagnostic classification. It is not dangerous to give electroplexy controlled by thiopentone and suxamethonium in the first month after confinement, provided there is no evidence of thrombophlebitis. In any subsequent pregnancy there is a one-in-five chance of recurrence. There is no psychiatric basis for advising a patient to avoid having another pregnancy for at least two years after her illness. Subsequent puerperal or non-puerperal illnesses tend to be of the same diagnostic type as the original puerperal illness, and the response to treatment similar. The only definite aetiological factor is the genetic make-up, but infection may be of some importance.

Some of these conclusions are in direct contradiction to statements in other surveys, the major disagreement being on the question of prognosis in those patients showing schizophrenic symptoms. Hemphill wrote that puerperal schizophrenia was a particularly malignant illness, only one of his 19 patients recovering sufficiently to live outside hospital: "Puerperal schizophrenia, in spite of favourable prognostic criteria, is rarely curable." Skottowe stated: "In schizophrenia the prognosis is grave, few patients recovering. The most that can reasonably be expected is stabilization at a level of invalidism necessitating some special care at home ; but nearly half of the patients in this group become more or less permanent mental-hospital patients, notwithstanding shock therapy." Boyd stated: "The diagnosis of schizophrenia implies a very serious

prognosis, and the majority of these patients progress to a severe mental deterioration." He felt, however, that the prognosis was slightly better than in schizophrenia occurring apart from childbirth. Brew and Seidenberg wrote: "The prognosis is somewhat poorer in the post-partum schizophrenic reactions than in these reactions in general." This pessimistic outlook is not shared by everyone, however. Mayer-Gross *et al.* (1954) wrote: "The prognosis for the first attack is relatively favourable as in other schizophrenias precipitated by physical illness." Foundeur *et al.*, from their experience with 50 post-partum schizophrenics, state: "It cannot be said that post-partum patients who were diagnosed as schizophrenic do less well than those with other diagnoses." Three out of four of their total group of 100 patients had a reasonable level of recovery four years after their hospitalization.

In view of these conflicting opinions, it is necessary to look critically at this series and at those previously published. The St. Patrick's schizophrenic group possibly comes from a better-off social class than other series. All the patients were married, and marital disharmony and home stresses, such as financial difficulties, were not much in evidence. Physical illness lending itself to correction was relatively frequent. The pre-morbid personality of the schizophrenic group was good. These factors all lend themselves to a good prognosis. In a group with a higher number of illegitimate pregnancies one would expect to find a higher incidence of unstable personalities in whom the prognosis would possibly be less good. Assessment by methods other than personal interview is open to fallacy. As the patients came from all over Ireland, and as the follow-up period was so long, personal interview with the patient was possible in only six of the 15 schizophrenic cases. In seven further cases there was information from the family doctor, and in one of the remaining two cases there was objective evidence from the husband.

Further evidence supporting the view that puerperal schizophrenia has an excellent prognosis is the fact that among the chronic female patients in St. Patrick's, the majority of whom are schizophrenics, there is no case in which the illness started during the puerperium. Moreover, it is the practice in the hospital to consider leucotomy in any illness in which a good remission cannot be obtained with other treatments, and when symptoms are persisting after two years. The records show that this has never been considered or performed in any case of puerperal psychosis. Undoubtedly before the era of active psychiatric treatment puerperal schizophrenia had a bad prognosis. This is amply documented by writers such as McIlroy (1928), James (1935), and Karnosh and Hope (1937). In those days, tuberculosis, pernicious anaemia, and many other diseases also had a bad prognosis, but the outlook has been completely changed by improvements in treatments. Modern psychiatric therapy such as electroplexy, insulin coma therapy, and the tranquillizing drugs, combined with an active social rehabilitation programme, undoubtedly does influence psychoses. Prognosis, therefore, can be assessed only in the light of the treatment given, and many authors, including Hemphill and Skottowe, give no details of intensity and duration of treatment.

There is general agreement that the great majority of patients with depressive illnesses recover, and that electroplexy is a very effective method of treatment. Hemphill, however, wrote: "There is a psychiatric entity—puerperal depression—which differs from the manic-depressive psychosis, and in many ways resembles involutional melancholia." He believes that both puerperal depression and typical manic-depressive cases respond poorly to E.C.T., although eventual recovery is to be expected. There is no evidence from this study to support the view that puerperal depression is a psychiatric entity. Moreover, the response to electroplexy was uniformly good, although some cases pursued a relapsing course.

The only follow-up study of the prognosis in subsequent pregnancies that I have been able to trace is that of White *et al.* (1957). Of their 100 patients 22 had a total of 27 additional pregnancies, but only three had a recurrence of their mental illness. They wrote: "From this small sample one might infer that the chances are that one in seven patients will experience mental illness associated with a subsequent pregnancy." Other authors give grave warnings of the dangers of subsequent pregnancies, but quote no supporting figures. Hemphill states: "It seems to be extremely dangerous for a patient who has recovered from puerperal schizophrenia to become pregnant again." Boyd concurs in a very similar phrase. The evidence from this study is that the risk of recurrence in any subsequent pregnancy is one in five. No particular diagnostic group seems more susceptible. Eight of the 15 schizophrenic patients had 13 subsequent pregnancies with only one associated puerperal psychosis. Unfortunately, no criterion by which recurrence may be forecast has been determined. Any recurrence is likely to follow the same pattern as the previous illness, and the response to treatment is likely to be similar. In the light of this knowledge no dogmatic statement can be made about the advisability or otherwise of avoiding further pregnancies. Each case must be decided on its own merits, taking into account the personality of the patient, the degree of desire for another child, and the pattern of the previous illness.

A past history of puerperal psychosis is, in the opinion of some authors, an indication for consideration of therapeutic abortion early in any subsequent pregnancy. Religious and ethical considerations forbid such a practice in Ireland. A recent discussion at the Royal Society of Medicine, London, revealed wide disagreement among psychiatrists about the value of and indications for termination of pregnancy (Pearce, 1957). The findings of this study lend no support to advocates of therapeutic abortion or sterilization. Moreover, termination of pregnancy does not seem to be without psychiatric risk. In 1955, in Sweden, where it is widely practised, Ekblad followed up a series of 479 women in whom abortion had been induced on psychiatric grounds. He found that 25% developed subsequent guilt reactions of varying severity. Siegfried (1951) is quoted as having found 59% of such reactions. Polonio and Figueiredo (1955), in a study of 244 puerperal psychoses in Lisbon, found spontaneous abortion responsible for 20% of the cases.

It would seem wise, in the individual case presenting early in a subsequent pregnancy, to inquire about marital stresses and home difficulties which might be alterable. Efficient antenatal care should be ensured, to minimize infection and anaemia. Encouragement and reassurance will often be necessary. Four patients in this series developed anxiety symptoms during ensuing pregnancies. These responded well to simple psychotherapy and mild sedation.

The conflicting views about psychoses associated with childbirth can be resolved finally only when large-scale studies with careful and personal follow-ups are undertaken. It would seem to be an eminently suitable and worth while subject for a Medical Research Council investigation co-ordinating the facts from a number of centres.

Summary

75 patients who had suffered from puerperal mental illness were followed up for periods varying from 4 months to 10½ years. Diagnosis, treatment, and results are analysed.

65 of the patients are now in normal health and only 2 have residual psychotic symptoms. None have become chronic hospital invalids. All 15 schizophrenic patients are fully recovered. The diverse views on the prognosis in puerperal schizophrenia are reviewed and discussed.

Electroplexy controlled by relaxants was given uneventfully to 12 patients within one month of confinement. It is considered to be safe, provided there is no evidence of thrombophlebitis.

The recurrence rate of puerperal mental illness in subsequent pregnancies in this series was 1 in 5 (18.7%). Relapse was not more frequent when the next birth occurred within two years of the illness.

Therapeutic abortion is discussed.

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ACUTE LARYNGOTRACHEOBRONCHITIS TREATED WITH 0.125% SUPERINONE

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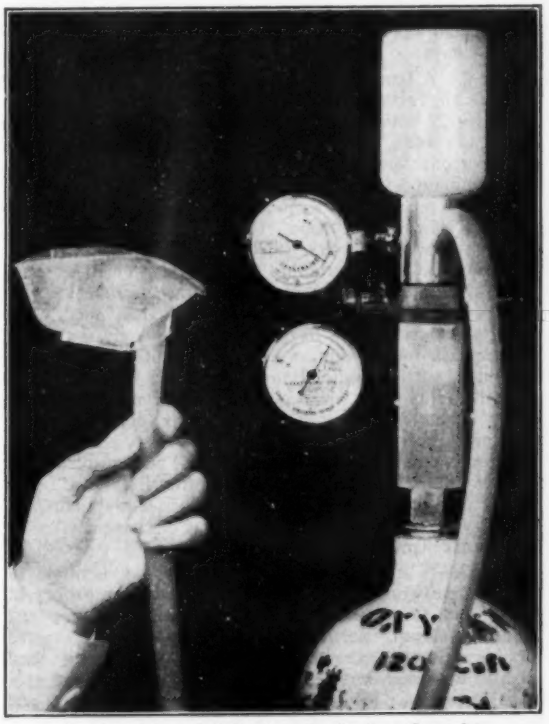
0.125% superinone is a surface-active agent which acts by lowering surface tension, causing liquefaction of thick mucoid and purulent exudations in the upper respiratory tract and bronchial tree. Thickening of the sputum and dryness of the respiratory membranes are minimized, permitting better ciliary action and thus facilitating expectoration. Superinone is made up in a sterile alkaline medium ("alevaire"), which is administered as an inhalation in the form of a fine mist produced by a nebulizer usually activated by oxygen. It may be given intermittently or continuously (see illustration).

Acute laryngotracheobronchitis is usually of sudden onset and often follows a mild upper respiratory infection. It may be rapidly fatal, death being due either to asphyxia caused by laryngeal obstruction with thick viscid mucus or to toxaemia. The infection is probably of virus origin (Rabe, 1948). Cytopathogenic agents have been isolated from the secretion of several patients (Beale *et al.*, 1957), and in a recent paper Beale *et al.* (1958) demonstrated that the presence of these bodies in cases of acute laryngotracheobronchitis is associated with a rise in antibodies during convalescence. Clinically the appearances are reminiscent of laryngeal diphtheria (Garson, 1950), and before the name laryngotracheobronchitis was coined many cases were thought to be due to this cause, though this diagnosis was never confirmed at post-mortem examinations.

The advent of chloramphenicol was of great value in dealing with the infection and toxaemia (Moncrieff and Weller, 1949), thus reducing the mortality; but the treatment of the asphyxia proved more difficult. Mild cases may be treated by steam inhalation if there is no evidence of bronchopneumonia, but as the patients are anoxic oxygen must be given as well. These patients



Apparatus for administering alevaire in a fine mist.

were therefore nursed in an oxygen tent, being transferred to a steam tent for 10 minutes every hour. Pharyngeal suction was carried out every 15–20 minutes. For cases with asphyxia bronchoscopic suction seemed rational, but this was not always possible and the manipulations involved could easily prove fatal. Tracheotomy then was the only means of trying to prevent death from asphyxia, but, although this successfully bypassed the obstructed larynx, one still had to deal with the viscid exudate in the trachea and bronchial tree. It was felt, therefore, that 0.125% superinone might be of use in dealing with this exudate, and the following is a report of five cases so treated.

Case Reports

Case 1.—A female infant aged 6 weeks was admitted to hospital on February 6, 1958, with a 24-hour history of a cough and cold. She had become very pale and short of breath in a few hours. The birth, personal, and family history revealed nothing relevant. On examination she was afebrile, but grey, cyanosed, and distressed, with rapid breathing and some subcostal recession. Air entry was good, with crepitations at the right base. Post-nasal mucus in small quantity was present. Penicillin was prescribed and the infant nursed in an oxygen tent. She became very much worse some 12 hours later, with marked respiratory embarrassment, collapse, and cyanosis. Air entry over the

lungs was then very poor and there was much white viscid mucus in the fauces arising from the larynx. A diagnosis of acute laryngotracheobronchitis was made. It was decided to give alevaire by facemask for 10 minutes every two hours, followed by pharyngeal suction. Penicillin was discontinued and chloramphenicol 125 mg. six-hourly substituted. After 12 hours there was no dypsnoea or cyanosis, and mucus was much reduced and less viscid. Air entry was then good, with no subcostal recession. The alevaire was finally discontinued after 48 hours and the oxygen tent removed. Chloramphenicol was stopped after five days. On admission the W.B.C. was 16,300. The chest *x*-ray picture on February 20 was clear. The baby was discharged quite well after 18 days.

Case 2.—A female infant aged 3 months was admitted to hospital on February 11, 1958, with a history of croupy cough for 24 hours. She became worse suddenly two hours before admission, with marked dypsnoea and cyanosis. The birth, personal, and family history revealed nothing relevant. On examination she was afebrile, collapsed, and limp, with moderate generalized cyanosis, much dyspnoea, and moderate subcostal recession. Faucial examination revealed much viscid white mucus arising from the larynx. Air entry was poor and few crepitations were heard. There were no other significant signs. Acute laryngotracheobronchitis was diagnosed and she was admitted to hospital at once. The infant was nursed in an oxygen tent and was given alevaire by facemask for 10 minutes every 90 minutes, followed by pharyngeal suction and chloramphenicol 125 mg. six-hourly. After 12 hours there was no dypsnoea or cyanosis, and the fauces were clear; the air entry over the lungs was good, with no subcostal recession. Her general condition was very good. Alevaire and the oxygen tent were discontinued after 48 hours and choramphenicol after five days. The W.B.C. on admission was 8,400. The chest *x*-ray picture on February 19 was clear. The infant was discharged after 19 days in excellent general condition.

Case 3.—A male infant aged 3 weeks was admitted to hospital on February 17, 1958, with a three-day history of cough and 12-hour history of cough with vomiting and cyanosis. Birth, personal, and family history showed nothing relevant. On examination he was afebrile and slightly cyanosed, with rapid respiration and marked subcostal recession. Air entry over the lungs was poor, and there was inspiratory stridor. A moderate amount of white viscid mucus was present in the throat. The infant was nursed in an oxygen tent and was given alevaire by facemask for five minutes every two hours, followed by pharyngeal suction and chloramphenicol 125 mg. six-hourly. The patient showed marked improvement in about eight hours. There was no dyspnoea or cyanosis, the fauces were clear, and air entry was good. The oxygen was discontinued after 24 hours, but chloramphenicol was continued for five days, by which time all abnormal signs had cleared. The W.B.C. on admission was 7,600. The baby was discharged after 11 days.

Case 4.—A male infant aged 4½ months was admitted to hospital on March 1, 1958, with a history of cough and snuffles for two weeks and pallor and cyanotic attacks for two days. A dyspnoeic attack occurred before admission. Birth, personal, and family history revealed nothing relevant. On admission the child was febrile, with only slight cyanosis and normal respiration, and did not appear to be seriously ill. Air entry over the lungs was good, with a few crepitations at the left base. A short time after admission, however, he became very distressed, pale, cyanosed, and limp. On examination there was very poor air entry with marked respiratory embarrassment. Faucial examination revealed a large quantity of viscid white mucus. Treatment consisted of immediate pharyngeal suction. Alevaire was given by facemask five minutes every two hours followed by pharyngeal suction, and chloramphenicol 125 mg. six-hourly was prescribed. There was marked improvement after about 12 hours: no dyspnoea or cyanosis, air entry good, and fauces free of exudate. The alevaire was discontinued after 36 hours, but the oxygen tent was needed for three days. Chloramphenicol was stopped after five days. Progress was complicated by a secondary bronchopneumonia, which, however, responded to tetracycline. Chest *x*-ray films showed a patch of consolidation at the right base which suggested abscess formation, but further films showed that this was resolving satisfactorily. This, of course, has prolonged the baby's stay in hospital. The W.B.C. on admission was 7,300.

Case 5.—A male infant aged 5 weeks was admitted to hospital on March 1, 1958, with a three-day history of cough and cyanotic and dyspnoeic attacks for the previous few hours. Birth, personal, and family history revealed nothing relevant. On examination he was cyanosed and dyspnoeic, with marked subcostal recession. Air entry over the lungs was very poor; there were no added sounds. A moderate amount of viscid white mucus was present in the pharynx. He was nursed in an oxygen tent and given alevaire by facemask for five minutes every two hours followed by pharyngeal suction and chloramphenicol 125 mg. six-hourly. Marked improvement occurred after a few hours: improved air entry, no dyspnoea or cyanosis, and fauces free of exudate. Alevaire was discontinued after 36 hours; oxygen was maintained for three days. Chloramphenicol was discontinued after five days, by which time all abnormal signs had disappeared. The W.B.C. on March 4 was 17,800. Chest *x*-ray examination on March 12 showed clear lung fields with some interlobar pleural thickening on the right side. He was discharged quite well after three weeks.

Comment

Cases 1, 2, and 4, would have qualified for tracheotomy, but it was decided to try the effect of alevaire before actually resorting to this. Previous attempts at diffusing alevaire into the oxygen tent continuously had not been successful, so it was thought advisable to administer it in Case 1 by means of a facemask placed directly over the patient's nose and mouth. The resulting liquefaction of the thick viscid mucus after only a few minutes, with rapid improvement of the asphyxia and cyanosis, was quite impressive, and so this method of administering alevaire intermittently was continued. Although the laryngotracheal secretion ceased to form after 8 to 12 hours, the intermittent administration of alevaire was continued for a longer period as described in the case reports.

Summary

Five cases of acute laryngotracheobronchitis are reported in which the asphyxial aspect was successfully treated with alevaire. Three of these (Cases 1, 2, and 4) would have needed tracheotomy otherwise. The alevaire resulted in rapid liquefaction of the viscid laryngeal exudate, with immediate improvement of the dyspnoea and cyanosis. All the patients recovered.

We thank the sisters and nursing staff for the excellent nursing management of these cases.

ADDENDUM.—Since the above was written Case 4 developed a recurrence of bronchopneumonia during his convalescence. His stools were then noticed to be frequent and very offensive. Examination of the stools showed no tryptic activity. No tryptic activity was detected in the duodenal juice, and his sweat test showed an increase in the chlorides to 840 mg./100 ml. There seemed no doubt, therefore, that he was suffering from mucoviscidosis. His condition continued to deteriorate, with increase in the physical signs over the lungs and reticular shadows in the chest *x*-ray films. Death occurred on April 25, 1958. Post-mortem examination revealed purulent bronchopneumonia and a tough fibrotic pancreas.

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POISONING BY ACONITINE

REPORT OF TWO CASES

BY

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The history of poisoning by aconite is a long one, going far back into ancient times. This is not surprising, since the plant species from which the poison is derived, notably *Aconitum napellus* (monk's-hood) and *Aconitum ferox*, are common and widely distributed. Within modern times, however, aconite poisoning has been relatively uncommon, certainly within the United Kingdom; and poisoning with the pure alkaloid itself, aconitine, is still more rare. For this reason the symptoms are worth recording, as they occurred in two recent non-fatal cases.

Two medical students, engaged in "spring-cleaning" a privately owned collection of materia medica, found in one of the cupboards a number of small glass phials labelled as containing various vitamin preparations. These they decided to throw out, but before doing so they each took a "pinch" from certain of the phials, including one from which a detached label, inscribed "vitamin C" appeared to have fallen. Subsequent investigation showed that the white crystalline powder in this phial was in fact aconitine, in a total quantity of about 250 mg. (4 gr.), but failed to reveal how the aconitine came to be in the collection or how long it had been there.

In an attempted assessment of the amount they had had, the students demonstrated exactly how they had taken a pinch of powder between finger and thumb, put it on the palm of the other hand and then transferred it to the tongue. Although an estimate arrived at in such a manner cannot be regarded as exact, it is based on more direct evidence than is available in many cases of poisoning, and the students' statements and demonstrations were consistent and convincing. From these it appears reasonably certain that each student had a dose of between 5 and 10 mg. (1/12–1/6 gr.) of aconitine, and more nearly the latter than the former. Both agreed that there was no great difference in the quantity of powder taken, but that Mr. B. (Case 1) probably had slightly more than Mr. T. (Case 2).

The aconitine was taken at 1.20 p.m., and the following is a description of the subsequent symptoms in each case.

Case 1

Mr. B. experienced a "sharp," slightly bitter taste, and a rapidly developing sensation of warmth and tingling in his tongue, which increased in intensity and extent until his whole mouth was affected. Within 10 minutes his tongue, cheeks, and lips felt numb and "drawn," his throat felt constricted, and he had a feeling of nausea. He gargled with water and took a large drink of water to make himself vomit. In this he was successful, and vomiting recurred at intervals during the next four hours without any further efforts on his part. Within half an hour of taking the dose, tingling and numbness had appeared in his fingers, and gradually spread "all over," but became particularly noticeable and distressing in his jaws and face. The vomiting, tingling, and numbness increased to a maximum about 4 p.m.—that is, some two and a half hours after taking the poison, and at this time he was conscious also of great tiredness and actual muscular weakness, so marked that he could only lie on his bed. In spite of his tiredness, however, he felt restless, the restlessness being attributable at least in part to a feeling that the sensory disturbances in the face and elsewhere were more distressing if he stayed still. From 4 p.m. onwards his symptoms abated gradually, and by the later part of the evening he felt quite fit and well again.

Case 2

Mr. T. experienced almost immediately a slightly bitter taste and a tingling, burning sensation in the tongue, mouth, and throat, which developed into a condition of numbness, tightness, and constriction, lasting till 2 p.m. At 2 p.m. he felt slight nausea and was salivating freely but did not vomit. Indeed, during the next hour his symptoms regressed and he felt fairly well. At 3.15 p.m., however, he began to experience a tingling sensation, which gradually pervaded all parts of the body, becoming especially marked in the face. By 5 p.m. this tingling and numbness in the face were very distressing; he had had three bouts of retching and vomiting; he felt very sick and salivated freely; he felt faint and very cold, especially in the limbs, and his voice seemed far away. His skin was cold and moist.

He had to lie down because he was so weak, and he could scarcely move his limbs. Voluntary effort to seek or call for assistance was impossible. Yet he felt restless, and again the restlessness was dictated in part at least by the feeling of apprehension induced by the numbness in his face, and elsewhere, which seemed to be worse when he lay still. Any attempt to get up, however, brought him near to fainting. He remained in this state for more than two hours, the symptoms of tingling and numbness, salivation, and sickness, coldness, and faintness, weakness, restlessness, and a feeling of dread all persisting and becoming even worse. During this period he repeatedly tried to feel his pulse, but it was undetectable. His illness reached its climax between 7 and 8 p.m., and from 8 p.m. onwards he improved gradually. About 11.30 he fell asleep. He slept soundly throughout the night and felt quite recovered the following day.

Comment

It will be recalled that Mr. B. had, if anything, a larger dose than Mr. T. From the relative severity of their illness it would appear probable that Mr. B. succeeded in getting rid of a proportion of the poison by means of his self-induced vomiting 10 minutes after the dose was taken and by the further attacks of vomiting soon afterwards. Mr. T. did not take the same precautions, nor did he have any vomiting for the first two and a half hours or so. Indeed, he was lulled into a false sense of security by the almost complete absence of symptoms between 2 and 3 p.m.

Neither student received any treatment, although they reported to the out-patient department of a hospital about 2 p.m. They were told to go home, lie down, keep warm, and return if they felt worse—sound enough advice so far as it goes, and perhaps reasonable in the circumstances at that time, although in the light of events it might well have been supplemented or replaced by more active measures and a period of observation. The students went from the hospital to their respective lodgings, where, as it happened on that particular day, they were obliged to endure in solitude what was, particularly in the case of Mr. T., a most unpleasant and alarming experience.

Identification.—The powder in the phial was submitted for chemical investigation. It was reported as being purely alkaloidal in character, and giving reactions which were consistent with its being aconitine. With the usual range of chemical tests for alkaloids it is not possible as a rule to be more specific than this when seeking to identify aconitine, and confirmation must be sought by means of physiological tests. The substance was personally sampled, perhaps slightly to excess, for not only was there a rapid development of warmth and tingling in the tongue and mouth, but this went on to numbness and tightness of the mouth and throat and tingling in the fingers, which persisted for some time. Finally a dose of 0.5 mg. (1/128 gr.) was injected

subcutaneously into a rat. After a delay of about a minute, the animal showed signs of restlessness and agitation, and started to run. Salivation, retching, and respiratory distress developed, followed by paralysis, affecting first the hind limbs and then the forelimbs. There were terminal convulsions before the animal died three minutes after being given the injection. These were the results on which the opinion was based that the material in the phial was in fact aconitine.

Discussion

The fatal dose of aconitine is variously stated as being anything from 1/60 to 1/10 gr. (1 to 6.5 mg.) or slightly more. The uncertainty on what constitutes a fatal dose is no doubt related to the infrequency of poisoning with the pure alkaloid and also to its unstable nature. Furthermore, there are several varieties of aconitine, and they are not all equally poisonous. Factors of this kind presumably explain why the results were not even more serious in the cases described, although in each case the dose was certainly in excess of that which is commonly regarded as fatal or potentially so.

Aconite (aconitine) has both a local or peripheral and a systemic or central action, and both have served as a basis for its use as a therapeutic agent. The local or peripheral effect is the more striking and characteristic—namely, tingling and numbness, experienced either on local application or in the mouth when ingested, and in the extremities after absorption. The drug was formerly used, usually in the form of the tincture, for the relief of neuralgic or rheumatic pain. The central effect of value was believed to be a slowing of the heart and a reduction in blood pressure, hence its former use in certain cases of heart disease and in various febrile conditions.

To-day aconite is very little used therapeutically, and never internally, except perhaps in homoeopathic practice. Aconite poisoning is therefore uncommon, and the occasional cases which do occur are usually due to the suicidal or accidental ingestion of a liniment containing aconite mixed with other noxious substances. Accidental death through mistaking monk's-hood root for horse-radish is less frequent to-day than it appears to have been some years ago.

Because of its rapid and rather striking local effects, aconite is not an ideal homicidal poison, and it has rarely been used as such in this country. It has been suggested, however, that because of the effects on the heart, coupled with peripheral effects experienced in the arms and hands, sickness, and upper abdominal discomfort, and an early fatal outcome, cases of homicidal aconite poisoning might well be overlooked and regarded as deaths due to coronary artery disease.

In an Irish case in the first half of last century (*Regina* v. *McConkey*, 1841), powdered aconite root (monk's-hood) was mixed with pepper and sprinkled over the greens which formed part of the victim's dinner. Dr. Pritchard (1864–5) gave tincture of aconite mixed with Battley's solution to at least one of his two victims, but essentially the deaths were due to antimony poisoning. The outstanding homicidal case is undoubtedly that of Lamson (1881–2), also a medical man of sorts, who administered the alkaloid aconitine in a capsule (or a cake) to his invalid brother-in-law.

In the Lamson case aconitine was detected in the vomit, in the urine, and in an extract from the stomach, stomach contents, liver, spleen, and one kidney. Identification was by means of alkaloidal reactions, by the local effects produced on the tongue, and by the rapidly fatal effects on mice. Since then various colour and crystal tests have been described in attempts to render the chemical identification of aconitine more positive, but there is no general agreement on the specificity of any such tests. It has been suggested that most reliance can be placed on the effects of aconitine on the frog's heart, which appear in a characteristic sequence—namely, initial slowing followed by sudden acceleration, then incoordination, and a final slowing and arrest.

Greater certainty may be possible with the more modern methods of chromatography and spectrophotometry. Curry and Powell (1954) have described a method for the detection of alkaloids on a micro-chemical scale by means of paper chromatography which would appear to be applicable in the case of aconitine. Similarly, Kaye (1954) has described a characteristic spectrophotometric absorption curve for aconitine. Since these methods are applicable to very small quantities of material they would, if proved to be sufficiently specific, provide an extremely valuable means of identification, and might indeed relegate the older forms of testing to a role which was largely confirmatory. It is certain, however, that the characteristic and striking local effects of aconite will always retain their highly diagnostic significance.

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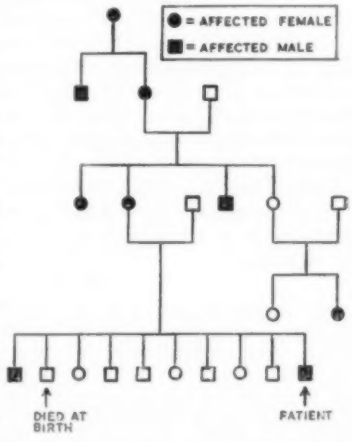
Medical Memoranda

A Case of Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus is a heredo-familial disease characterized by polydipsia and polyuria from infancy. It is a sex-linked condition affecting males usually and transmitted by females, who act as heterozygous carriers. The condition is resistant to treatment with "pitressin," and appears to be due to an inherent kidney defect which results in failure of tubular reabsorption of water. Renal function in all other respects is unaffected. The following is a report on a case occurring in a youth of 18. This case is of interest because some of the female members of his family, besides acting as carriers, appear to have suffered from the full-blown clinical syndrome.

Case Report

The patient complained that he had had to drink large quantities of water and passed large amounts of "white urine" for as long as he could remember. He found it necessary to carry supplies of water with him on train journeys or when he visited the cinema. Failure to relieve his thirst resulted in drowsiness, headache, and general malaise. He passed urine every half to one hour during the day and four to six times during the night. His daily intake and output was between 12 and 16 litres of water.



He was one of 10 children who were all alive except one brother who died at birth. He had five living brothers and three sisters. His mother, eldest brother, a maternal aunt, a maternal uncle, a female cousin, maternal grandmother, a maternal great-uncle, and maternal great-grandmother all suffered from this syndrome from birth. The family tree showing the incidence of the disease in the two sexes was compiled from information given by the patient and his mother. The latter stated that she found it necessary to take 6 pints (3.4 litres) of water to bed with her at night and drank much more during the day.

The general appearance of the patient was normal and there were no abnormal physical signs in any system.

Special Investigations.—The specific gravity of the urine varied from 1000 to, on one occasion, 1012. More usually it was between 1004 and 1008. It was not possible to carry out a urine concentration test, as the patient could not be deprived of water for a sufficient length of time. M.S.U.: reaction acid; protein nil; reducing substances nil; deposit N.A.D.; cultures sterile. The blood urea was 32 mg./100 ml. Serum electrolytes were within normal limits. *X*-ray films of the chest and skull were normal. The Wassermann, Kahn, and Price precipitation reaction were negative.

At first twice-weekly injections of 5 units of pitressin in oil were given intramuscularly. This, however, had a negligible effect in reducing the polyuria. The patient did feel that pitressin snuff administered four or five times daily reduced his frequency slightly, but this was not enough to render its continued use worth while. It can be concluded, in this case, that pitressin by the intramuscular or nasal route had no appreciable effect in reducing diuresis.

COMMENT

This case is of interest in that females appear to have exhibited the fully developed clinical syndrome. This feature is unusual. Recent published work has shown that symptomless female carriers of the disease show an impairment of urine-concentrating power and a lowered response to pitressin (Garrod, 1956). Carter and Simpkiss (1956) investigated four families and showed that the female carriers were unable to concentrate urine beyond 1018. They suggested that this test be used as a means of "carrier state" detection.

My thanks are due to Lieutenant-Colonel R. M. Johnstone, R.A.M.C., for his kind permission to publish this case.

L. H. GLASER, M.B., B.S.

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Duplication of the Stomach Simulating Pyloric Stenosis

Duplication of the stomach is an uncommon condition. Gross (1953) reports two cases in a series of 68 duplications of the alimentary tract studied by Dr. Sidney Farber at the Boston Children's Hospital. One, in a child of 7 years, gave rise to symptoms of epigastric fullness and discomfort and a palpable mass in the epigastrium, but did not produce obstruction. The cyst was as large as the stomach, and lined by necrotic mucosa. Treatment by partial excision and marsupialization was successful. His second patient, aged 3 days, had a cyst 4 cm. in diameter, lined by gastric mucosa, on the greater curvature of the stomach. Excision of the cyst and gastrostomy were performed, but the baby died. Galloway, Sutherland, and Williams (1956) report a case, first seen at the age of 4 weeks, with symptoms of vomiting, green slimy stools, and failure to gain weight. A swelling was visible in the left hypochondrium moving downwards when the baby was fed. Peristalsis was not seen. The vomiting was not severe, and operation was postponed until the baby was 4 months old. The cyst measured 5 by 3 by 3 cm., and was attached midway along the greater curvature. It was lined with gastric mucosa. Complete excision of the cyst was carried out and the baby made a good recovery.

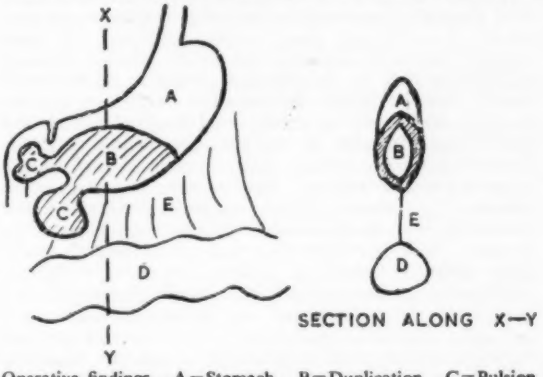
The following case presented with symptoms and signs suggesting pyloric stenosis.

CASE REPORT

A male child, the second baby of healthy parents, was born on September 22, 1956, by caesarean section, and weighed 10 lb. 3 oz. (4.6 kg.) at birth. He was breast-fed for the first month and did not vomit during this time. At the age of 4 weeks he was put on to feeds of full-cream National dried milk, and a week later he started to vomit about half of every feed. The vomits were projectile in character, and he became constipated. On admission to hospital on November 17, at the age of 8 weeks, he weighed only 8 lb. 13 oz. (4 kg.).

On examination he was thin and slightly dehydrated. His stomach contained 1 oz. (28 ml.) of residue immediately before a feed. During feeding visible gastric peristalsis was seen, and a large firm mobile tumour was felt in the right hypochondrium. He was given small frequent feeds of half-strength Hartmann's solution, which he retained. His dehydration was corrected, and he was fit for operation on November 19.

Operation was performed by Mr. A. C. Gairdner. The pylorus was found to be normal. The pyloric antrum was obstructed by a pyriform swelling which formed part of the



Operative findings. A=Stomach. B=Duplication. C=Pulsion diverticula. D=Transverse colon. E=Gastrocolic omentum.

greater curvature of the stomach. This swelling had a common muscular wall with the greater curvature of the stomach, and was a blind gastric duplication consisting of secreting gastric mucosa and muscular tissue which was grossly hypertrophied. The wall common to the stomach and the swelling was also grossly hypertrophied, and it was this which caused the obstruction. In two places the mucosa had become herniated through the muscular wall, forming pulsion diverticula (see Diagram). The wall of the subsidiary stomach was excised with the diverticula, leaving the common wall, from which the mucosa was completely removed. The remaining hypertrophied stomach wall was then found to be still partly obstructing the pyloric antrum, so a posterior gastro-enterostomy was performed.

The specimen consisted of five pieces of cyst wall, the largest measuring 3.5 by 1 cm. and 0.5 cm. thick. The walls consisted of thick muscle, lined by gastric mucosa. The fluid contained in the cysts was colourless and slightly opalescent, containing 6 g. of protein per 100 ml. Unfortunately tests for acid and pepsin were not performed.

Post-operative Progress.—Fluid requirements were given by scalp-vein infusion for the first four days, together with a transfusion of 100 ml. of blood. Feeds of half-strength Hartmann's solution were begun 48 hours after operation, expressed breast milk being substituted on the fourth day. His recovery was uneventful, although he was slow in gaining weight. His birth weight was not regained until the age of 3 months (4½ weeks after operation), but he then gained a further 13 oz. (370 g.) in the next 10 days.

A barium-meal examination on February 18, 1957, three months after operation, showed that the meal passed into the small intestine both via the pylorus and via the gastro-jejunostomy.

When seen on June 27, seven months after operation, he was very well, with no vomiting, his weight at the age of 9 months being 20 lb. 12 oz. (9.4 kg.).

I am grateful to Dr. F. S. W. Brimblecombe and Mr. A. C. Gairdner for permission to record this case, and to the nursing staff of the Royal Devon and Exeter Hospital for their care of the patient.

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Reviews

AORTOGRAPHY IN RENAL DISEASE

Aortography. Its Application in Urological and Some Other Conditions. By W. Barr Stirling, Ch.M., F.R.C.S.(Ed.), F.R.F.P.S.G. (Pp. 292+vii; illustrated. 50s.) Edinburgh and London: E. and S. Livingstone Ltd. 1957.

This monograph of about 290 pages relates the author's experiences of some 500 aortograms performed mainly for renal disease. Some vascular and other conditions are considered in a relatively short terminal section. The early chapters contain an account of the history, applied anatomy, and technique of the examination performed by the translumbar route. There is an interesting chapter on pressure factors in the aorta. In a lucid account of the hazards and possible complications of the procedure, anuria following repeated injections, without extravasation of the contrast medium, has been omitted. The congenital variations of the renal tract and the importance of the blood supply are well illustrated and described and their surgical aspects are stressed. While the application of the investigation to polycystic disease is limited, not everyone would agree that the appearances are not specific. It is also refreshing to find that, in the author's opinion, the differentiation of simple cyst from cortical neoplasm is reliable, when the opposite view has recently been stated in the literature. I entirely endorse the author's opinion. The importance of the examination in the assessment of function and distribution of blood supply in hydronephrosis, renal calculus, and other conditions requiring reparative or conservative surgery is stressed and beautifully illustrated. In suspected renal hypertension, especially if the excretory pyelogram is normal, the examination may nevertheless reveal arterial insufficiency to the whole of part of one kidney. The book is well endowed with short case reports. As the author states in the preface, this monograph is not a textbook; nevertheless it is sufficiently comprehensive to form a basis for those interested in the examination and its possibilities.

C. G. WHITESIDE.

CHROMATOGRAPHY TECHNIQUES

Chromatographic Techniques: Clinical and Biochemical Applications. Edited by Ivor Smith, B.Sc., Ph.D., F.R.I.C. (Pp. 309+ix; illustrated. 45s.) London: William Heinemann Medical Books, Ltd. 1958.

Paper chromatography represents one of the most important advances in biochemical technique, and it has justly been given pride of place in the exhibition of British inventions at the Brussels World Fair. In medicine it has the particular advantage of using small quantities of material. It can be carried out without elaborate equipment and can be performed even by those who have not been highly trained. The widespread application of the technique has resulted in numerous papers distributed amongst a great variety of journals. It is often not possible to employ these methods without doing some additional research of one's own. Their reliability will have to be verified, and technical details more often than not have to be modified. A laboratory bench-book on chromatography techniques is, therefore, a most useful addition to the armamentarium of the medical laboratory worker. The title of the book is a misnomer. Chromatographic methods include adsorption chromatography in columns made of silica gel, alumina, and ion-exchange resins. These techniques are either not described or only mentioned in passing. The editor, Dr. Ivor Smith, is a postgraduate lecturer in chromatographic methods at the Technical College, Acton, London; he is also associated with the Courtauld Institute of Middlesex Hospital, London, and he is joined by J. P. Jepson, R. W. H. Edwards, A. H. Snaith, and H. G. Stevens from the Middlesex Hospital. Other contributors are J. V. Jackson from New Scotland Yard, T. Wood from Bovril Ltd., H. G. Horsewell from May and Baker Ltd., E. Kawerau from St. Mary's Hospital, and M. Birchenough from the Norwood Technical College, London. Amino-acids and amines, imidazoles, purines, sugars, the acids of the citric acid cycle, barbiturates, and steroids are amongst the compounds which are considered in detail. A most valuable contribution is that dealing with the indoles, including hydroxyindolylacetic acid and tryptamine. It is perhaps surprising, but presumably owing to the book's restriction to paper chromatography, that the useful work by Huisman and his colleagues on resin chromatography of haemoglobin variants is not mentioned. There are also chapters on chromatographic apparatus and techniques and two indexes—one general, dealing with more than 500 items, and the other of some 600 compounds named in the tables.

Considering the number of tables, diagrams, and illustrations, and the quality of the paper, the book is not expensive. It will undoubtedly become a standard laboratory bench book, and the authors and publishers are to be congratulated for having made a substantial contribution to laboratory practice.

H. LEHMANN.

ANATOMY AND HUMANISM

Anatomist at Large: An Autobiography and Selected Essays. By G. W. Corner. (Pp. 213. $4.00). New York: Basic Books. 1958.

Professor George Corner's eminence is well recognized in both anatomical and physiological circles. Distinction between the two departments, on the level on which he works, has indeed now almost vanished, but he is specially known for his discoveries on the sexual cycle of apes, which closely resembles that of the human subject. Thus much of his work is, or will be in the near future, of direct medical application. He was born at Baltimore in 1889, and has spent there most of his active life as student, investigator, and teacher. After a sound basic education he entered Johns Hopkins University, first "majoring" in classics and afterwards changing to science, especially biology, finally passing to a medical course. He was a pupil of the anatomists F. P. Mall and Florence Sabin, to whom he gives special acknowledgment. His clinical years were in the latter period of first blossoming of that great school, where William H. Welch, William S. Halsted, Howard A. Kelly, and Whitridge Williams were among his teachers. After several crowded years, which included a time spent in Germany and two seasons with the Grenfell Medical Mission in Labrador, where he met his accomplished wife, he spent a year in Great Britain with Starling, Bayliss, and Elliot Smith, finding time somehow to produce a distinguished piece of historical research, a line of work in which he always showed, and still shows, much interest. After acting as assistant to Herbert M. Evans in California he became professor of anatomy at Rochester, N.Y. There he remained until his return to his native city to occupy a research chair provided by the Carnegie Fund. In 1952 he was Eastman Visiting Professor at Oxford, when he was elected into the Royal Society. Soon after he became president of the American Philosophical Society. On retiring from his chair at Baltimore he undertook to write the history of the Rockefeller Foundation, on which work he is still engaged.

In addition to the autobiography, this volume includes a "type research" in substantially its original form. It is a happy idea to republish such a work, for, better than any other, it gives the reader a view of the investigator's real preoccupations. For this purpose he has selected his classical paper in which, with one of his students, he showed experimentally that the corpora lutea contain a specific hormone, a function of which is to induce pregestational proliferation of the endometrium in preparation for reception of embryos. He calls it "Search for a Hormone," and its results have elucidated the human menstrual cycle.

The lives of experimentalists are notoriously uneventful outside the laboratory, but Dr. Corner is exceptional in having had a richly varied career which has always been

coloured by humane purposefulness. In reading his essays one feels that the man is best reflected in his several addresses to students. They are the work of a scientist who, in his labours, has never lost sight of their possible application to medical practice. Here is none of the remoteness of the traditional professor. These student addresses especially maintain the dignity of a fine literary tradition. They reveal much of the personality of the author, who, in his turn, must surely have felt their delivery as a call and a charge. They show Professor Corner as a wise and experienced physician in the true Hippocratic mood, for "where the love of Man is, there also is love of the Art."

CHARLES SINGER.

PATHOLOGY IN THE U.S.A.

Pathology. Edited by W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P. Third edition. (Pp. 1,402+xv; illustrated. £6.) London: Henry Kimpton. 1957.

The third edition of this standard textbook follows the general plan of its predecessors. Some parts have been completely rewritten, others revised, and a few shortened. The references have been brought up to date and the number of illustrations increased, and the binding appears to be more sturdy. As there are now 35 contributors, representing 17 of the 48 stars on the Union flag, "Anderson" can be regarded as fairly representative of the healthy state of pathology in the United States. Great Britain and the London Hospital are represented by one author, Professor Dorothy S. Russell, who contributes an article on the pituitary gland. In the words of the editor, "a thorough coverage of the subject has been attempted within the limitations of a single volume." The reader will agree that this attempt has been singularly successful and the editor's purpose achieved by the exceptionally liberal use of small print. Few, if any, single-volume modern textbooks contain so much accurate and relevant pathological information. Dr. Anderson suggests that the large-print sections can be used by the junior student, and that he will increasingly need the "small print" as he progresses. There is no doubt that the book will continue to serve as a reliable reference book for advanced students, clinicians, and pathologists. While "morbid physiology" is by no means neglected, the background of this book is the accurate correlation of descriptive morbid anatomy and histology with clinical signs and symptoms. This interpretation of the word "pathology" in the United States is very probably related to the firmly established and highly commendable practice of holding clinico-pathological discussions on the majority of patients who die in their teaching hospitals. It is not improbable that we are tending to neglect this approach in Great Britain.

GEOFFREY HADFIELD.

WHITLA'S DICTIONARY OF TREATMENT

Whitla's Dictionary of Medical Treatment. Ninth edition, by R. S. Allison, V.R.D., M.D., F.R.C.P., D.P.M., and T. H. Crozier, M.D., B.Sc., F.R.C.P., and twenty-six contributors. (Pp. 854+xiii. 52s. 6d.) London: Baillière, Tindall and Cox. 1957.

This is the ninth edition of a book which first appeared in 1891, and the authorship has grown from a single man to 26 contributors. It is now the product of the Belfast school as a whole. While the authorship has increased, the territory covered has diminished; surgical topics have been omitted and the material is confined to medical therapeutics. The arrangement is alphabetical, and in general the items can be classified in four groups—the names of recognized diseases or syndromes, common presenting symptoms and signs, therapeutic procedures, and finally therapeutic principles underlying medical treatment. There are a detailed list of contents and a good index, so that the book is easy to read. The book is addressed to the senior student and practitioner, and does what it sets out to do extremely well. The instructions are modern and practical, and there are none of those relics of a bygone day which so often intrude in texts of this age. Common diseases like coronary thrombosis are well handled. There is an excellent section on the painful lesions of the neck, arm, and shoulder, which are apologetically classified under the heading "brachial neuritis." Prescriptions are given in both the English and the metric system, but figures for the latter have been so literally translated that they would be extremely annoying to the chemist. For example, 15 minims becomes 0.9 ml. instead of 1 ml., and the equivalent of a dose of ½ oz. is given as 14.2 ml. instead of 15 ml.

L. J. WITTS.

INTRACTABLE HEADACHE

Management of the Patient with Headache. By Perry S. MacNeal, M.D., F.A.C.P., Bernard J. Alpers, M.D., Sc.D.(Med.), F.A.C.P., and William R. O'Brien, M.D., F.A.P.A. (Pp. 145. 26s.) London: Henry Kimpton. 1957.

Intractable headache or frequently occurring headache is not an uncommon problem in most types of medical practice. To those concerned with questions of differential diagnosis and of treatment this little book may be of some interest, and even perhaps of limited value. The attainment is uneven, as might be expected when such a wide subject is tackled by multiple authorship. The sections dealing with psychopathology and with the personality traits of the migrainous sufferer are frankly unconvincing, naive, and unacceptable. One feels at times tempted to protest, like Oscar Wilde: "You must not find symbols in everything you see. It makes life impossible." With much of what the authors have to say about the medicinal treatment of migraine—both in and between attacks—no one can quarrel, and many medical men will indeed appreciate the clear exposition of the present position of drug therapy. Some of the *obiter dicta* are shrewd: . . . "History is far and away the most important part of the study of a patient with headache. The physical examination helps some [*sic*] and laboratory studies least of all. The skull *x*-ray, ordered so frequently, is almost uniformly a waste of time and money. We have seldom seen a simple *x*-ray study of the skull reveal anything of importance in the study of the patient with the chief complaint of headache." None the less the wise physician will continue to utilize routine radiology, not only of the skull but also of the chest, in the investigation of his patients with intractable headache.

MACDONALD CRITCHLEY.

THE ADRENALS IN DIABETES

Cortico-surrénale et Diabète Humain: Relations entre le Diabète Stéroïdien et le Diabète Ordinaire. By P. Bastenie with eight contributors. (Pp. 506; illustrated. 4,000 frs.) Paris: Masson et Cie. 1956.

This is a comprehensive review of the role of the adrenals in human diabetes. Virtually the whole range of human diabetes is discussed, from the rarer syndromes of the Cushing and Achard-Thiers type to the more commonly occurring disease encountered in everyday clinical practice. The earlier part of the book has chapters devoted to the basic physiology and biochemistry of diabetes, and these are exhaustively dealt with. Succeeding chapters are concerned with methods used in investigating the metabolism of glucose and steroids and the fate of steroids in man. After chapters dealing separately with acromegaly and Cushing's syndrome, space is devoted to the classification of human diabetes. Some interesting analogies are drawn between the obese type of human diabetes (the Continental *diabète gras*) and Cushing's syndrome on both clinical and experimental grounds. The possible part played by the adrenal cortex in the genesis of diabetic vascular complications is discussed at length, as is both the surgical and medical therapy used in this condition. The volume is well produced, with some good diagrams and clear photographs. Even though at times it is provocative, this book, with its wealth of references, will be very valuable to clinicians and research workers alike in this highly controversial field.

K. W. TAYLOR.

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IMMUNOLOGICAL SPECULATIONS

The skin is a well-recognized mirror of systemic diseases. Initial observations on lupus erythematosus and sarcoidosis stemmed from dermatologists; but, later, specialists in other disciplines were to contribute to the evolution of knowledge. The first step forward was the recognition that they were not primarily dermatological curiosities, but instead disorders frequently affecting tissue systems throughout the body. Once this was established, the terms disseminated, systemic, and generalized were bestowed to include manifestations remote from the original skin disease. Thus far, study of the diseases had been a meeting-point for the dermatologist, general physician, and pathologist. But it became evident that the diagnosis could be made with some confidence in the absence of skin lesions. Although the field of interest of the physician had now eclipsed that of the dermatologist, he still relied on the morbid anatomist for corroborative histological evidence of the "onion-skin" and "wire loop" vascular lesions found respectively in the spleen and renal glomeruli in lupus erythematosus.

Emphasis is once again shifting, this time from the histological to a more dynamic immunological approach to these and other disorders. Acute lupus erythematosus gives clinical, histological, and haematological evidence suggesting a hypersensitivity mechanism. E. G. L. Bywaters[1] and W. Dameshek[2] have suggested that this may be of the auto-immunization variety. The severe constitutional upset with fever, polyarthralgia, serositis, nodules, lymphadenopathy and also the peculiar vasculitis observed histologically have for long suggested an allergic response, similar in some respects to serum sickness and drug allergy. To this picture may be added a set of associated haematological disturbances—haemolytic anaemia, leucopenia, thrombocytopenia, and coagulation defects. That these are linked with a positive Coombs test, the L.E. cell factor, platelet agglutinins, false-positive serological tests for syphilis, iso-agglutinins after blood transfusion, and raised serum gammaglobulin levels all support the thesis that an immunological disturbance is responsible. Dameshek considers that these clinical, histological, and haematological features of systemic lupus erythematosus portray the end-result of a series of reactions directed against the endothelium of blood vessels and against red corpuscles, white cells, platelets, and blood-coagulation factors. In our present degree of ignorance of these reactions the speculation is a reasonable one and it is certainly fashionable to confer the term "auto-immune" on a set of reactions which apparently arise within the host's own body and attack various constituents of his own tissues. It remains to be seen whether a responsible antigenic substance is uncovered. Hydrallazine is known to produce a syndrome resembling lupus erythematosus, and the L.E. cell has also been detected in the serum of patients with hypersensitivity reactions to penicillin. It is possible that these or similar chemicals may so alter the cell surface as to render it antigenic.

Another factor which might be usefully entertained in discussing the pathogenesis of disseminated lupus erythematosus is its conspicuous predilection for women of the child-bearing years of life. In fact, Dameshek[2] states that he has observed it only in three males, two of whom had received hydrallazine and the third penicillin, all for prolonged periods. He suggests that the active endometrium is an ideal milieu for the production of antigenic substances from altered blood cells and blood vessels, associated as it is with large pools of stagnant blood. He also suggests that the periodic character of the catamenia might play a significant part, corresponding to "booster" injections in an immunization procedure or sensitization process. Although this stimulating concept cannot at present be verified, it does not preclude us from attempting to analyse our data of other ill-defined conditions in a similar light. Sarcoidosis has been mentioned as a dermatological curiosity which was extended to become a disorder of general medical interest. Radiology and tissue biopsy provided means of establishing the diagnosis in the absence of skin lesions. The occurrence of fever, polyarthralgia, erythema nodosum, and acute iritis at its onset, the depression of delayed-type (tuberculin-type) skin-test reactions, the abnormal serum globulins, and the Kveim test phenomenon could all be construed as evidence of hypersensitivity or of reticulo-endothelial imbalance. G. Teilum[3,4] brackets both disseminated lupus erythematosus and sarcoidosis as examples of allergic hyperglobulinosis. Moreover, erythema nodosum due to sarcoidosis also predominantly affects women during the reproductive years of life. For the present these may appear to be a series of unlinked observations, but an immunological approach holds the exciting promise of a connecting thread.

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[2] Dameshek, W., *Ann. intern. med.*, 1958, **48**, 707.
[3] Teilum, G., *Amer. J. Path.*, 1948, **24**, 389.
[4] —— *Acta path. microbiol. scand.*, 1951, **28**, 294.

SYMPTOMLESS JAUNDICE

If the serum of apparently normal blood donors is analysed for bilirubin content, a proportion will be found above the normal upper limit of 1 mg. per 100 ml. A few of these subjects will be suffering from congenital spherocytosis (acholuric jaundice), which is readily diagnosed by examination of the peripheral blood film, reticulocyte count, and erythrocyte fragility tests. An even smaller number will be shown to suffer from a well-compensated Laennec's cirrhosis, and other stigmata of liver disease such as vascular spiders on the skin, hepatomegaly, or splenomegaly will often be found. Sero-flocculation tests such as thymol turbidity may be positive, and injected bromsulphalein is usually retained abnormally. There remains the group of congenital hyperbilirubinaemias which are now attracting much general interest. The most frequent is Gilbert's disease,[1 2] which is inherited as a dominant characteristic. Mild jaundice with tiredness and languor are noted intermittently. There are no other abnormal physical signs. Histological examination of liver biopsy material shows normal appearances.[3] Bile pigment is not present in the urine. J. F. Crigler and V. A. Najjar[4] have described what is probably a more severe form of Gilbert's disease in which jaundice is deeper. The circulating serum bilirubin is unconjugated with glucuronide (" indirect " type) and has an affinity for nervous tissue, so that the features of kernicterus are present. A biochemical defect in the conjugation of bilirubin with glucuronic acid in the liver has been demonstrated in deeply jaundiced patients with the Crigler–Najjar type.[5] The specific defect seems to be in glucuronyl transferase, an enzyme which is present in hepatic microsomes and which transfers glucuronic acid from uridine diphosphate glucuronic acid to various receptors, including bilirubin.[6] The liver in Gunn's strain of congenitally jaundiced Wistar rats has been shown to have a similar defect.[7] Diminution of conjugation of other substances with glucuronic acid has also been shown: these include menthol, salicylates, and metabolites of cortisone.[5 8 9] The patients and the rats were much more icteric than the usual sufferer from Gilbert's disease. Difficulty has arisen in confirming these results in the mildly icteric, and more recently it has been shown that patients with Gilbert's disease conjugate administered salicylamide[10] and also menthol[11] with glucuronic acid normally. Nevertheless the demonstration of a specific hepatic enzymatic defect in the severe forms of the disease represents an important advance, and results of the wider application of these methods to other forms of jaundice will be awaited with interest.

The third, rarer, form of congenital hyperbilirubinaemia was first described in 1954 by I. N. Dubin and F. B. Johnson[12] as " chronic idiopathic jaundice with unidentified pigment in liver cells " and by H. Sprinz and R. S. Nelson[13] as " persistent non-haemolytic hyperbilirubinaemia associated with lipochrome-like pigment in liver cells." Dubin has recently reviewed 50 cases of the disease.[14] The disorder differs from the Gilbert type in that the circulating bilirubin is conjugated with glucuronide (" direct " type) and is water-soluble and so appears in the urine. The essential defect is not in the conjugation of bilirubin but in its excretion into the bile. The main point of distinction is in the liver, which, macroscopically, is greenish-black. Dubin[14] has even suggested that the disease might be termed " mavro-hepatic icterus " or " black-liver jaundice." The pigment is found in liver cells and belongs to the family of lipofuscins, the so-called " wear and tear " pigments. It has not been chemically identified.

Both Gilbert's and the Dubin–Johnson type of congenital hyperbilirubinaemia carry an excellent prognosis. Their distinction one from the other remains of theoretical rather than clinical interest. The differentiation from the more serious types of chronic intermittent jaundice is, however, of great practical importance and merits the fullest biochemical and haematological investigation, perhaps necessitating aspiration liver biopsy.

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2 Meulengracht, E., *Quart. J. Med.*, 1947, **16**, 83.
3 Krarup, N. B., and Roholm, K., *Klin. Wschr.*, 1941, **20**, 193.
4 Crigler, J. F., Jr., and Najjar, V. A., *Pediatrics*, 1952, **10**, 169.
5 Schmid, R., *et al.*, *J. clin. Invest.*, 1957, **36**, 927.
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11 Isselbacher, K. J., 1958, personal communication.
12 Dubin, I. N., and Johnson, F. B., *Medicine* (*Baltimore*), 1954, **33**, 155.
13 Sprinz, H., and Nelson, R. S., *Ann. intern. Med.*, 1954, **41**, 952.
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TISSUE BUILDING AND PROTEIN ANABOLIZERS

The metabolic pool is a useful concept, allowing us to make a mental image of the circulating fluid to which nutrients, hormones, vitamins, and degradation products each add their quota and from which at any hour of the day or night, in each deviation from health and in all the seven ages of man, the body seeks to supply its varying demands. Even if we narrow our field of vision to the best understood of the products of metabolism, glucose,[1] we soon find that ignorance outweighs understanding, and if we press our inquiry as far as the uptake and utilization of glucose by the cell mystery enwraps us. As to the metabolism of proteins, the situation is even less accurately defined: we know that growth requires an increased amount of protein, and we can measure

this by the amount of nitrogen retained in the body. We know, too, that in certain katabolic states—accident, operation, inflammation, and neoplasm—an increased amount of protein is broken down and utilized in unusual ways, by gluconeogenesis, for example, and we can in these conditions measure the increased loss of nitrogen from the body. When the body enters the stage of protein repair, then nitrogen is retained in excess until complete restitution occurs. Hormonal agencies such as the protein anabolizers, growth hormone, and the androgens control the build-up of protein. Cortisol is recognized as the main protein katabolizer, and in his Burns lecture D. Hubble[2] attempted the construction of a hormonal formula for the metabolism of protein. Although the balance may be tipped in either direction in disease states, yet we have to assume that the body each hour in each day maintains its predestined balance between protein building and protein breakdown, and no one would wish lightly to interfere with it.

In many disease states, however, there is great protein loss, and the need for increased protein anabolism is often seen. In recovery from acute illness,[3] from operations,[4] from accidents,[5] and from severe burns[6] it is rational therapy to encourage as rapid a protein build-up as can be obtained. Since the growth hormone is not available for protein anabolism in man, testosterone in some form can be employed for this purpose. This has the disadvantage, when used in women and children, of a strongly virilizing action, and effective alternative preparations with a much weaker androgenic action than testosterone have been long awaited. The synthesis of the 19-nortestosterone group (" nilevar " and " durabolin ") is a step towards meeting this need, for the protein-anabolizing effect of these compounds is equal to that of testosterone and the virilizing effect is said to be slight. It has, however, been stated recently that these new compounds definitely cause virilism,[7 8] though they are markedly less androgenic than testosterone. When, therefore, they are used for long periods in women and children such undesirable consequences must be carefully looked for. Methyl testosterone has for many years been available for use as a stimulus to protein anabolism in men, and it is salutary to remember, while welcoming the new and expensive remedies, how little it has in fact been used in supportive therapy.

Fuller Albright[9] first described the anti-anabolic action of the glucocorticoids on protein metabolism—an action which produces some of the most characteristic of the symptoms of Cushing's syndrome—and suggested the use of testosterone in therapy. There are to-day much more effective treatments for this disease, but if for any reason surgery is contra-indicated and *x*-ray therapy fails then the new protein anabolizers should be used. With long-continued therapy by cortisol or any of its associated compounds in moderate or high dosage it is rational—particularly in children to assist growth and in post-menopausal women to prevent osteoporosis—to use the 19-nor-testosterone derivatives. There are other indications for the use of the protein-anabolizers. Since we have no growth hormone for therapeutic use, these new remedies should be valuable in hypopituitary dwarfism and might also be tested in other forms of dwarfism.[10] Stimulation of growth by testosterone has to be undertaken with great care because of its androgenic effect, but this hormone has been used with some success in the treatment of carcinoma of the breast with dissemination to bones. This good effect has been attributed to a consequent change in the hormonal environment of the cancer, possibly resulting in some depression of oestrogen action by testosterone. If this is so, no good result would be expected from the use of 19-nor-testosterone in this disease, and the manufacturers of nilevar, while recommending its use in carcinomatosis as a stimulant to protein metabolism, expressly disclaim for it any specific action on bone metastases. In another common disorder, osteoporosis in women, oestrogens have been shown to be effective in treatment[11]; methyl testosterone has also been used as an additional therapy in small doses and in interrupted courses. If, for any reason, it is necessary to supplement the action of oestrogens, then 19-nor-testosterone should be used.

The therapeutic indications for these new protein anabolizers are, then, in stimulation of growth in the dwarfed of both sexes, in aiding the recovery of women and children from any illness in which there has been severe protein loss, whether acute or chronic, and in protecting the skeleton against the harmful action of the glucocorticoids. The cost of one week's treatment by nilevar may be from £3 to £5 (more than seven times as expensive as the equivalent treatment by methyl testosterone), and an expenditure of this sort, especially if long continued, may be thought justifiable only when an express need for the treatment is apparent.

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THE NATURE OF PENICILLIN SENSITIVITY

Reactions to penicillin may be of two kinds. In one, skin manifestations predominate, whether the reaction is due to contact or to parenteral injection: they are of urticarial type and, if extensive, are accompanied by fever. The second and more dangerous kind of reaction is immediate shock, which if not immediately treated may be fatal within a few minutes. The fact that sensitivity can manifest itself in two quite different ways requires explanation, and emphasizes the importance of understanding the basis of these states. A test for sensitivity may sometimes be desirable, and various methods have been used. S. Swift[1] suggests a scratch test, followed by intradermal injection if the former is negative. He describes two kinds of reaction, an immediate one denoting the anaphylactic type of sensitivity, and a delayed reaction seen in patients with sensitivity of the urticarial or "serum sickness" type. Not everyone has had such consistent results, and several authors complain that patients who have exhibited sensitivity fail to react to such tests. O. Idsöe and P.-N. Wang,[2] reporting on reactions to penicillin in Taiwan (Formosa), give the results of skin tests for sensitivity performed on 48 of 106 patients in whom reactions occurred to the subsequent injection: these tests had been negative in all patients developing severe or even fatal shock, and positive only in a proportion of those with milder shock or urticaria. On the other hand, there is the opposite difficulty of an unduly violent reaction to a test. P. S. Mayer and his colleagues[3] caused shock with a test dose of only 10 units.

According to Swift, sensitivity is passively transferable, which would signify the formation of an antibody, and, since penicillin while in the blood stream is to some extent bound to plasma albumin, it has been supposed to function as a haptene. If indeed antibody formation is the basis of sensitivity, the antibody should be demonstrable. Two recent papers make the claim that this has been achieved. R. J. Muelling and colleagues[4] carried out an investigation on 100 patients who had exhibited sensitivity either to penicillin or to one of several other antibiotics. They tested for antibodies in the serum of these patients by the method of diffusion in a gel, the serum being incorporated in agar at the bottom of a tube and covered with a layer of agar separating it from a solution of the antibiotic: lines of precipitation appearing in the intervening layer indicate the presence of antibody. Of 71 sera from patients suspected of penicillin sensitivity, 34 gave positive results. A few positive results were also obtained with several other antibiotics, including even tetracyclines, to which sensitivity is reputed to be very rare. There are some strange features in these findings, notably the long delay which seems sometimes to have occurred before a precipitate appeared (it is said to be advisable to continue the test for 21 days) and the occurrence of double bands when in fact the antigen is a single one. Nevertheless other workers will doubtless wish to explore this method of detecting antibody.

The other observation, reported by Allyn B. Ley and her colleagues,[5] of New York, is more positive and immediately significant. It arose from a chance finding. The serum of a patient requiring transfusion was found to agglutinate every suspension of red cells to which it was added. These had been preserved with penicillin. Fresh cells from the same individuals were unaffected, and, on the other hand, cells of any blood group to which penicillin had been added became agglutinable by this serum. The examination of about 2,000 further sera revealed 25 more possessing this property. All the people from whom they were obtained had at some time been treated with penicillin, but "only a minority" had exhibited penicillin sensitivity. To sensitize cells to the antibody in these sera they had to be suspended in rather high concentrations of penicillin: a 25% cell suspension required 3,000 units per ml. for 24 hours or higher concentrations for a shorter period. Admixture with concentrations of the same order deprived serum of the capacity to agglutinate sensitized cells, presumably owing to binding of the antibody. It was also found possible to elute the antibody from agglutinated cell suspensions by heating to 54° C. The clinical significance of this antibody remains to be determined, but its discovery provides another test which should certainly be applied in cases of clinical sensitivity, and may well stimulate a search for other methods of detecting the changes on which sensitivity depends.

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PEPTIC ULCER AND SECRETOR STATUS

That the occurrence of peptic ulcer is associated with blood group O is now well established. Results obtained from over 12,000 patients with peptic ulcer indicate that the risk of duodenal ulcer is about 38% more and the risk of gastric ulcer about 19% more for subjects with blood group O than for other subjects.[1] While the increased risk is, thus, not great, it has been observed in eight countries, and it is difficult to believe that the association could be an artifact due to the existence of strains within each national population who were both high in group O and particularly susceptible to peptic ulceration. In fact, the blood group antigens (group substances A, B, and H in persons of blood groups A, B, and O respectively) are mucopolysaccharides and form an important proportion of the mucins normally secreted in the gastro-intestinal tract, so that it would be reasonable to suppose that the association between blood group and disease was a direct result of a difference in the local physiological effects of the different substances. Not all persons, however, secrete the ABH substances, and if this hypothesis were true it might be supposed that non-secretors would be more susceptible to the disease than secretors. Moreover, in these circumstances, it would be expected that a

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[3] McConnell, R. B., and Sheppard, P. M., *Acta genet. (Basel)*, 1956, **6**, 574.
[4] Wallace, J., Brown, D. A. P., Cook, I. A., and Melrose, A. G., *Scot. med. J.*, 1958, **3**, 105.

difference in the susceptibility of persons of different groups would be found only among those whose gastro-intestinal mucus contained some of the relevant group substance. These possibilities were first investigated by Clarke and his co-workers at Liverpool,[2 3] and, as was expected, the proportion of non-secretors among duodenal ulcer patients was found to be greater than among a control group of healthy subjects (35.0% against 24.2%). But, contrary to expectation, the proportion of group O subjects was found to be just as great among the non-secretors with ulcer as among the secretors. This result has now been confirmed by J. Wallace and colleagues.[4] Among 181 subjects with duodenal ulcer belonging to blood groups A, B, and AB the proportion of non-secretors was 37.0%, against 23.5% among a control group of patients with non-gastro-intestinal disease, whereas among group O subjects the proportions were 39.5% and 28.7%. It seems, therefore, that the greater susceptibility of group O subjects is independent of the presence of the H antigen in the mucous secretions, and the association between blood group and disease can hardly be regarded as due to a direct local effect. Further evidence that this is not the explanation is provided by the data on the distribution of blood groups within ulcer families. C. A. Clarke and R. B. McConnell's most recent data were reported at the symposium on medical research, Wisconsin University, on April 7–10 last. They have now studied nearly 400 duodenal ulcer sibships, and, though these show some slight predominance of group O subjects and of non-secretors among the ulcer patients in comparison with their healthy sibs, the excesses are very slight. These workers have therefore felt obliged to suggest that a maternal factor might be involved, and that mothers who are group O may be more likely to produce children who will develop a duodenal ulcer than mothers belonging to any one of the other groups.

Obscure though the explanation now is, the recent data on secretor status provide the most encouraging clue to the aetiology of peptic ulcer that has been obtained for many years. Taken in conjunction with the data on distribution of blood groups, they point to a factor of considerable importance. For it can be shown that the risk of developing the disease among non-secretors who belong to group O is nearly 2.5 times as great as among men whose mucous secretions contain the A or B antigens, and, according to Wallace and his co-workers, the relative risk of developing an ulcer severe enough to warrant operation may be even higher.

THE JOHN CURTIN SCHOOL

In March the permanent building of the John Curtin School of Medical Research was officially opened. The school, situated in Canberra, is the fourth of the Australian National University's research schools, the others being those for the physical sciences, the social sciences, and for Pacific studies.[1] Founded in 1946, the National University is Australia's answer to the old complaint that so many of her ablest scientists are lost to universities and research centres abroad, a complaint that was perhaps particularly justified in the case of medical scientists. Other Australian scientists had the many fine laboratories of the Commonwealth Scientific and Industrial Research Organization, whereas the only native medical research centre with an assured international reputation was in those days the relatively small Walter and Eliza Hall Institute in Melbourne. The opportunities for the new school, under its dean, Professor A. H. Ennor, are thus great.

Appropriately it was Sir Howard Florey who performed the opening ceremony, in the presence of a distinguished company which included the Prime Minister of Australia, for it was Sir Howard's recommendations to the Government of the day that supplied the critical stimulus for the school's birth. In 1944, in a report to the Commonwealth Government, he recommended the setting up on Australian soil of a national institute for advanced medical sciences, and the John Curtin School is the direct result of this suggestion. Later, when his proposal had become accepted policy, Sir Howard Florey guided the school's development. In 1948, when the first professor was appointed, it had no laboratories of its own and its various departments therefore began by being housed in accommodation generously lent by other institutions—the department of biochemistry at the Commonwealth Serum Laboratories, Melbourne; the department of medical chemistry at the Wellcome Research Institution in London; the department of microbiology at the Walter and Eliza Hall Institute; the department of experimental pathology in Sir Howard Florey's laboratories in Oxford; and the department of physiology at Otago University. By 1951 temporary laboratories were ready in Canberra, and the departments were set up there until their move last year to their permanent home. At present the total research staff is about 40 and there are some 20 Ph.D. students, but the school is still in the process of growth, both in the sense that over the next few years several new departments are projected and in the sense that each department has yet to reach its own maturity. The new building provides first-rate facilities for research in a wide range of the medical sciences, and already the John Curtin School has earned itself a name known throughout the world.

BLACK PATCH DELIRIUM

Mental illness occasionally follows a surgical operation, just as it may follow childbirth, often after a short interval, and the symptoms may be those of mania, depression, or a schizophrenic state.[1] More rarely the mental symptoms are those of a confusional state, and may come on immediately, particularly in the elderly and arteriosclerotic. Since operations for cataract are performed predominantly on elderly patients, it is not surprising that "cataract delirium" or "black patch

[1] *Med. J. Aust.*, 1958, **1**, 677.

[1] Stengel, E., Zeitlyn, B. B., and Rayner, E. H., *J. ment. Sci.*, 1958, **104**, 389.
[2] Solomon, P., Leiderman, P. M., Mendelson, J., and Wexler, D., *Amer. J. Psychiat.*, 1957, **114**, 357.
[3] Weisman, A. D., and Hackett, T. P., *New Engl. J. Med.*, 1958, **258**, 1284.

delirium" should be well known to ophthalmologists. It appears to be due to the fact that both eyes are bandaged after operation. The temporary total blindness leads to disorientation, with restlessness, suspicion, and anxiety as its commonest signs. This is reminiscent of the temporary mental disorders that have been induced in volunteers by keeping them in darkened, soundproofed rooms, their limbs completely covered, so that sensory stimulation was minimal.[2] But in the patients submitted to surgical treatment of the eyes the confusional state is more easily produced, perhaps because of a degree of concomitant deafness or dementia. A. D. Weisman and T. P. Hackett[3] have reported cases in which the risk of a confusional state was averted by brief psychotherapy before operation. The psychiatrist endeavoured with each patient to establish himself as a recognizable individual in a recognized place, and used not only talk, but the scent of flowers, touch, and taste, to get into a warm relationship with the patient. He reappeared after the operation to remind the patient of orientation in space and time, and to reassure him on the successful outcome of treatment.

CONTRACTUAL VALIDITY OF SPENS

The Secretary of State for Scotland has refused to join with the B.M.A. in testing the contractual validity of Spens under Scottish law. The legal procedure in which the Minister had been asked to join with the B.M.A. was that of presenting a special case to the Court of Session. A special case is a device, peculiar to Scottish law, which enables parties amicably to agree to put their differences of opinion to the Court for an objective decision. The procedure was one which appeared particularly apt for settling, so far as doctors in Scotland were concerned, in an atmosphere of good will far removed from that of the usual type of contentious litigation, the divergence of views between the profession and the Government on the proper interpretation of the Spens Committee's recommendations. And the Chairman of Council's announcement[1] to the Representative Meeting at Birmingham that the Minister had been asked to participate was received with enthusiasm. The Secretary of State's refusal, as reported in this week's *Supplement*, can be only interpreted as another example of the Government's distaste for any calm and objective discussion of the Spens Reports.

IN NEED OF HELP

The generosity of individual doctors has enabled the Royal Medical Benevolent Fund to grow over the years, but, as its latest report says, "the necessity has also grown appallingly." Expenditure last year is witness to this; it was £51,194, leaving a surplus of only £132. Many cases of desperate need among doctors and their families are beyond the reach of State or other aid, and here the R.M.B.F. is indispensable to relieve their distress. A new venture is the purchase of a house in Putney for conversion to five self-contained flats to accommodate indigent doctors.

All doctors are urged to contribute what they can to help their unfortunate colleagues through this charity. By signing a seven-year covenant the Fund's income can be substantially increased without further cost to the subscriber, and there are also other ways in which the Fund and its ally, the Ladies' Guild, can be helped; full details of them can be obtained from the Secretary of the Fund at 1, Balliol House, Manor Fields, Putney, London, S.W.15.

ANNUAL CLINICAL MEETING AT SOUTHAMPTON

In the *Supplement* this week we print the programme of the Clinical Meeting which is being held in Southampton from December 4 to 7. This will be the first Annual Clinical Meeting to be held following the approval by Council of the Organization Committee's proposal[1] that a second scientific meeting should be held each year in addition to the Annual Meeting. The variety of the subjects chosen for the panel discussions and general sessions can be seen from the programme, and anyone who attends all the meetings and some of the clinical demonstrations will have had a concentrated refresher course presented in the most agreeable way possible. Not only will there be easy ways to learning through colour television and film shows, but during the afternoon of Friday, December 5, the American Medical Association's winter meeting in Minneapolis will be linked by telephone with the B.M.A.'s meeting in Southampton for the purpose of a transatlantic clinical conference: this novel event will no doubt have its entertaining as well as instructional aspects. Perhaps before Southampton welcomes an Annual Clinical Meeting for the second time transatlantic conferences may be linked by vision as well as sound. The local organizers of the meeting under the chairmanship of Dr. R. S. Russell-Smith have arranged what should prove to be an excellent clinical meeting, and on the social side too there will be much to enjoy in a short time. In every way it seems that Southampton is setting an admirable example to other towns which may be the venue of future Annual Clinical Meetings.

Members of the British and Canadian Medical Associations will receive with regret the news in this week's *Supplement* that their President-Elect, the Duke of Edinburgh, will be unable to be present at the Joint Annual Meeting of the two Associations in Edinburgh in July, 1959, since he will be with the Queen in Canada for the whole of that month.

Sir Arthur Porritt has agreed to act as chairman of the committee to review the medical services which is being set up under the joint sponsorship of the Royal Colleges, the Scottish Royal Medical Corporations, the British Medical Association, the College of General Practitioners, and the Society of Medical Officers of Health.

[1] *Brit. med. J., Supplement*, 1958, 2, 80.

[1] *Brit. med. J.*, 1958, 1, 1171.

A SURVEY OF 100 CONSECUTIVE CHILDREN AWAITING ADMISSION TO A MENTAL DEFICIENCY HOSPITAL

BY

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AND

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Owing to the acute shortage of beds in mental deficiency hospitals, the problems connected with long waiting-lists are becoming more serious. Parents may have to wait several years before they are offered a place for their child. The Fountain Hospital, of 600 beds, usually admits children under 5 years ; in theory they should be transferred in early adolescence to other mental deficiency hospitals, but, owing to the limited provision for adult low-grade defectives, the number of transfers is small. A few children improve enough to be accepted for educationally subnormal schools or schools for the handicapped, etc. (Kirman, 1958 ; Craib and Woodward, 1958). Vacancies also occur when children go home on licence, die, or move to other branches of this hospital. The area covered by this survey included south-east London, south-west London, and Surrey, thus presenting the problems of both town and country.

The aim of the survey was to assess the social and psychological problems associated with young defectives awaiting admission. Statutory supervision is carried out by the local authority while the defective child remains at home, and the present practice is generally for the home to be visited by the hospital social worker when a vacancy is being considered. Out-patient appointments are made when the parents particularly request this.

Method

The Fountain Hospital is situated within the London area, and in 1948 the administration was taken over by the South-West Metropolitan Regional Hospital Board. Owing to the need for these children to be visited regularly and the demand for beds for young defective children, arrangements were made to admit children from the London administrative areas outside the jurisdiction of the regional board. Vacancies are allocated between the areas, and additional vacancies are credited to the individual regional hospital boards which arrange transfers to adult hospitals for patients becoming too old to remain in this hospital. Of those still awaiting a vacancy there are over three times as many from one area as from the others. In our visiting, therefore, it was not surprising that many of the most urgent cases were found in this one area.

The survey deals with 100 consecutive names on the hospital waiting-list. The period covered was from September, 1955, to May, 1957. A combined visit was paid to the home by the social worker and psychologist, after making a written appointment. In the present inquiry this visit was made much earlier than usual. The ordinary hospital pre-admission form was completed by the social worker with the mother. This form is designed to obtain medico-social information about the child's early history together with his physical development, any previous hospital treatment, and the family circumstances. The precipitating factors which led the parents to ask for admission were noted and the psychologist tested the child and discussed his early development and present abilities with the mother.

Material

At the time of writing 50 of the 100 children no longer required a vacancy at this hospital: 12 had died, 21 had been admitted to other M.D. hospitals, 8 were no longer considered mentally deficient, 5 were able to stay at home, and in 4 cases the parents had moved from the catchment area. Of the remaining 50, 39 were still waiting admission and 11 had been admitted or offered a vacancy.

In 64 cases the reasons the child needed hospital care were discussed with the parent or guardian. These 64 cases included the 50 still on the waiting-list or admitted, plus 14 who later had their names withdrawn for reasons such as death or admission to other hospitals. In each case the main precipitating factor was assessed as well as any additional factors ; these are given in Table I. Some of these factors need further amplification.

Factors Precipitating Request for Admission

	Main	Additional
(1) Physical care of the defective had become too much for the mother	18	7
(2) Parents wanted the defective's name retained on the waiting-list for the future	13	0
(3) Defective in the care of the children's officer	7	0
(4) Parents concern over the adverse effect on their other children	6	13
(5) Hospital care considered necessary for defective or the child removed at birth	5	10
(6) Parents abroad	4	0
(7) Family illness or birth of a further child	3	6
(8) Defective's behaviour was disturbed or destructive	3	1
(9) Marital disharmony	3	1
(10) Housing difficulties	1	8
(11) Parents considered that the defective needed hospital training	1	0

(1) In most cases it appears that it is the physical strain of looking after the child that precipitates a request for admission. Some of these children are heavy and helpless, and the strain on the mother becomes too much. When temporary care can be arranged (up to a maximum of eight weeks), this sometimes enables the mother to keep the child at home. For many mothers in this group there is the added emotional strain of having a severely handicapped child ; the extent of this could not be assessed in a single interview.

(2) A number of parents realized that they would not always be able to care for the defective at home, and some felt the security of having the child's name retained on the waiting-list in case an emergency arose.

(3) Seven of the children have no home, are illegitimate, or have been abandoned. Whilst awaiting admission these children are placed in a nursery or foster home by a children's officer.

(4) For many normal children a defective sibling is an embarrassment and a tie, and the mothers cannot give them as much time and attention as they need. Although the main precipitating factor is rarely the welfare of other children, nearly a third of the parents were considering their needs when asking for admission.

(5) Some of the most tragic families are those where the parents, having been told soon after birth that the child is mentally deficient, are then strongly advised to apply for immediate hospital care. In three cases the child was separated from the parents when 2 weeks old and was then transferred to a private nursery while waiting for a hospital vacancy. The hydrocephalic child and the mongol child are particularly prone to such circumstances. The hydrocephalic child may need more medical and nursing care than can be given at home, but the baby mongol presents no nursing problem in normal circumstances. In the families in this group where the mongol baby has been separated at 2 weeks, serious emotional difficulties in the parents have arisen. Some parents who were unable to afford a private nursery have later expressed their thankfulness at having given their child a period of home care during his early life. Only a small proportion of parents felt it was " right " for their child to be away from them. From the point of view of the child's emotional needs, a hospital for mental defectives is no adequate substitute for the individual care given by a mother.

The remaining precipitating factors are self-explanatory; it will be noted that housing difficulties hold a relatively low position, although they appear to be an important subsidiary factor.

Psychological Tests

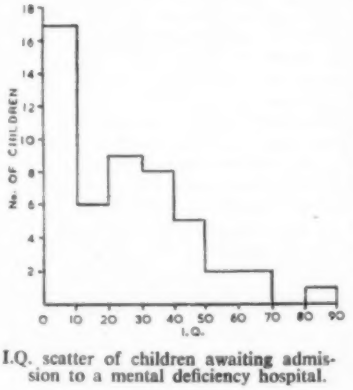
This survey was planned so that the children could be tested by a psychologist before they were admitted to a mental deficiency hospital, enabling them to be seen in their homes with their mother present. This was found to be helpful, as the mother was often able to describe the young child's achievements very accurately. However, directly speech was used to any considerable degree in testing, mothers found it difficult not to encourage the child, rephrase the question, or give the answers. From the mother's point of view, she could discuss the child's abilities on a developmental type of test with interest and very little guilt, but directly the child was asked to do specific items or to name objects, several mothers made remarks such as, "I haven't been able to teach him that yet," or, "Should I have done that with him?" or a more defensive and aggressive reaction was given such as, "Well, he couldn't do that because he's never played with things like that before." This last was said referring to test material which is usually new to a child.

Some of the mothers of mongols and gross idiots were very pleased to have their child tested; mothers of these children with rather obvious defects sometimes felt that insufficient time had been spent examining the child's abilities. Before this survey was carried out it was not appreciated how helpful a test can be to a mother in recognizing for herself the approximate level her child has reached and in realizing that, although his development is slow, it is progressing along the same lines as that of other children.

In spite of the advantages of testing in the home, it seems preferable that the parents should visit the hospital, bringing the child as an out-patient, and that testing should be carried out by a psychologist then, leaving the social worker to visit the home alone. With a small group of children who show disturbed behaviour, however, it might be very valuable to see them in their own homes, as their behaviour sometimes appears to change markedly on admission.

The testing was carried out to find the I.Q. scatter in 100 children awaiting admission and to investigate any who might later be considered educable. But, for the reasons already given, testing of the whole 100 was found to be impossible, so that the children described are the 50 remaining on the waiting-list or already admitted.

The children were tested with the Griffiths mental development scale and/or the Vineland social maturity scale, except for one mongol of 7 who was given a Terman – Merrill revision of the Sturford–Binet test, Form L. Where two tests were given the scores were averaged. This is of course not standard practice, but was suitable for the purpose of this survey. The results are given in the Chart.



I.Q. scatter of children awaiting admission to a mental deficiency hospital.

The average I.Q. of this group was 25, with a range from 2 to 84. All the children with I.Q.s over 50 were mongols. The average age of all the children on June 30, 1957, was 2.9, with a range from 3 months to 7 years. It was found that these children divided naturally into four groups—mongols, other imbeciles, idiots, and a group of children who showed severe behaviour disturbances and were consequently very difficult to assess accurately. In the whole group there were over three times as many boys as girls, the numbers being 38 boys and 12 girls. The ratio between boys and girls in each group was two to one for mongols and imbeciles, four to one for idiots, and eight to one for disturbed children. With such small numbers the high ratio for disturbed children can only be suggestive; the other ratios are similar to those usually found. The I.Q.s, I.Q. range, average ages, and age ranges of the various groups are given in Table II.

TABLE II.—*I.Q. and Age of Four Groups of Children Awaiting Admission*

Group	No.	I.Q.		Age in Years	
		Average	Range	Average	Range
Disturbed	9	31	17–49	4·25	2·42–5·67
Idiots	20	7	2–16	2·75	1 –5·08
Imbeciles	9	30	25–40	2·83	1·75–4·5
Mongols	12	45	13–84	2·33	0·25–7
Total ..	50	25	2–84	2·92	0·25–7

Of the 50 children tested in this group 12 were mongols, 20 were low-grade idiots, and 9 were imbeciles. These groups showed no marked behaviour problems; however, the nine remaining children showed severe emotional symptoms. The behaviour of these disturbed children might be due to brain damage, psychosis, emotional disturbance, or deafness, or any combination of these. They appeared to be physically fairly normal, although a little undersized. Their behaviour was characterized by restlessness, mannerisms, screaming attacks, perseveration, and avoidance of contact with people, although they sometimes made contact with their parents. The histories of these nine children were investigated, and in three cases there had been a disturbed background, early separation, or neglect, but in the other six there was no obvious explanation; the child had been at home with apparently well-adjusted parents and had normal siblings. It was decided to assess the backgrounds of the remaining children. Each child was considered in alphabetical order and put into one of two groups: those who had been separated from their mother for over three months, who had been abandoned, or whose parents showed signs of neurosis were described as having an abnormal background, while those who had spent all their lives in a stable home were described as having a normal background. The results are given in Table III. It will be seen that the homes of the disturbed children are no less stable than the others.

TABLE III.—*Number of Children Coming from Normal and Abnormal Homes in Each Group*

Group	No.	Normal Home	Abnormal Home
Disturbed	9	6	3
Idiots	20	13	7
Imbeciles	9	4	5
Mongols	12	6	6
Total ..	50	29	21

Discussion

It is realized that this division into "normal" and "abnormal" is rather arbitrary, that there may be hidden factors which have been overlooked, and that in some cases the child's original deficiency may have caused the abandonment, long hospitalization, etc.; however, nearly half the children in this group have had enough in their upbringing to justify disturbance, and the disturbed children's background does not appear to differ from the others. This was contrary to what was expected, and might be due to the smallness of the numbers, or the disturbed behaviour being caused by other than environmental factors. This does not detract from the possibility of individual children functioning on a defective level for no other reasons than emotional ones.

The high incidence of children with disturbed backgrounds is due to this group being selected because, for the various

reasons given above, their parents felt it best for them to come into hospital care. However, nearly all the parents seen wished strongly that they could have managed to keep their child at home.

The further study of differences between behaviour at home and behaviour in a new environment such as a hospital may prove of use in distinguishing the components of this probably mixed group who show disturbed behaviour.

The earlier home visit was found to be useful for several reasons. Firstly, to give the parents the opportunity of discussing their individual anxieties about the hospital with the hospital social worker. These anxieties are very varied, and include advice on allowance, delays in admission, emergency provisions, visiting arrangements, sick-notice procedure, availability of medical advice, legal implications, clothing, and provision of toys, as well as the child's future placement. In some cases the parents are not sure whether they want a vacancy, and wish to discuss this with the hospital social worker in order to clarify their ideas on hospital care.

Secondly, the visit was useful to correct any serious misunderstanding regarding the child and his hospital treatment. As patients naturally wish their child to be "cured" and some hope for curative treatment, it is necessary to explain to them that, although research is being carried out, as yet it is unwise to expect any cure. It is important to correct misconceptions such as that mongols usually die at 5 years of age and that the children are kept permanently in bed. Before visiting the hospital the parents may not realize the essential differences between this hospital and one for general medical treatment. With increasing awareness of mental deficiency in society, it is now rare for the parents to confuse mental illness with mental deficiency, but when this occurs it is important to clarify the position before the child is admitted.

Thirdly, at this home visit an out-patient appointment can be suggested, and this provides an opportunity for the parents to consult a specialist and see the hospital, and for the child to have a pre-admission assessment by a psychologist. This psychological test is useful as an early record and for research purposes. It also affords an opportunity for eliminating educable children from the waiting-list; it has been found that they are more likely to succeed if they go straight to school instead of having to adjust to an initial period of hospital care.

Lastly, an earlier visit is useful in making known the specialized services and experience of the hospital. These include arranging friendly contact between parents of waiting-list children and parents of those already admitted, and giving general advice on training and feeding when requested. Some of the parents felt that their normal home care for the child might be inadequate; one parent was very worried because, despite the fact that her child had a good set of teeth, she could not teach him to chew, not realizing that this was quite usual. Most of the parents were aware of the provision of temporary care, but wanted to know exact details from someone working in the hospital.

There was a discrepancy from area to area in the ways in which parents had been helped. Where statutory supervision is carried out by trained social workers the parents appeared to be more adequately informed of the implications of hospital care. Nevertheless there was still a need for a direct personal contact between the hospital and the parents. This would almost certainly lead to closer co-operation in future years.

In spite of the advantages of an earlier visit a difficulty is presented by the fact that out of the 100 consecutive cases 50 were withdrawn for various reasons. Nevertheless it is considered that the earlier visit would help the parents to adjust to the various problems relating to having a defective child. Likewise, the pre-admission testing by a psychologist would be found most valuable, not only in assessing the child's abilities but also in observing his behaviour in relation to his parents.

Summary

One hundred consecutive cases awaiting admission to a mental deficiency hospital for children were investigated. Joint home visits by a social worker and psychologist were paid to find the factors precipitating the request for admission, to test the child's intelligence, and to assess the usefulness of an earlier home visit by the social worker. In spite of the extra time involved, the value of an earlier visit was thought to be considerable. The children were found to divide into four categories, their I.Q.'s and age ranges are given, and a review was made of their home background. Out-patient visits to the hospital for examination and psychological testing are recommended, with home testing only in special circumstances.

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ISRAEL MEDICAL ASSOCIATION

FOURTH WORLD ASSEMBLY

[FROM A SPECIAL CORRESPONDENT]

The Israel Medical Association held its fourth world assembly at Tel Aviv from August 12 to 24, under the chairmanship of Dr. J. BICKELS. Great Britain was represented by Dr. E. E. LIEBER. The inaugural ceremony was attended by both the Prime Minister of Israel and the Minister of Health. Dr. S. WAND, Chairman of Council of the B.M.A., attended the last two days of the meeting, and was made an honorary member of the Assembly.

Professor Zondek's Address

Welcoming the overseas delegates, Professor HERMAN ZONDEK said that, though they might see in Israel problems and disease entities bearing the stamp of local climatic, nutritional, and social conditions, it would be absurd to speak of a national or specifically Jewish medicine. There was, however, an intimate connexion between the teaching of Judaism and the ethical aspects of medicine. The *Old Testament* message, Man is made in the image of God, imposed for the first time the moral obligation to respect the sanctity of life, a postulate that formed the ethical foundation of their profession. In the spirit of this tradition Jews had always shown a marked affinity to medicine, and for centuries this attitude had been instrumental in leading a disproportionately great number of Jews to the study of the natural sciences and to the medical profession.

Professor Zondek then turned to the scientific aspects of medicine. What had been their contribution to the philosophy underlying the profession of medicine? Not so long ago scientific thought had been largely dominated by the mechanistic doctrine of causality, reflected in such trends as rationalism, materialism, Darwinism, naturalism, and so on, until the human organism had been converted into a soulless machine. However, deeper insight into the workings of Nature had given a new direction to natural philosophical thought. In their lifetimes they had been privileged to witness the enormous strides made by the physical sciences, and not least by medicine; and yet they had not come a single step nearer to solving the essential riddle of life. Some examples from his own field of research would illustrate what he meant. "When I was a young assistant at the Charité in Berlin, nearly fifty years ago," said Professor Zondek, "the question cropped up whether the ganglia of the heart were responsible for the movement of the heart muscle or whether the latter possessed an inherent capacity for its activity as advocated by Ludwig and my teacher His. I still remember the crucial experiment which, at the time, roused much comment. A small piece of embryonic chicken

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heart, certainly devoid of nerve substance, was put into a test-tube and suspended in Carrel's solution. After a while it began to contract in the rhythm of the normal heart beat." The cause of the alternating contraction and relaxation which the heart relentlessly keeps up for decades was thus inherent in the heart muscle. Yet the eternal question stood, Why does a piece of tissue spontaneously start functioning at a given moment to stop without apparent cause?

The physician of our time, no matter to which school of thought he might adhere, was called upon to take a greater part in public life than hitherto. Humanity in our time was sick, suffering from numerous endogenous ailments—moral, political, and economic threats to its very existence—the most dangerous of which was the unchaining of atomic power. Humanity would no more get rid of that great threat. It seemed easy to die with the atomic bomb, but how should one live with it? Medicine was at a loss to devise a remedy, but doctors could contribute by an educational effort to increase respect and reverence for the miracle and sanctity of organic life.

Selected Scientific Papers

The second day was devoted to various papers on health progress in Israel. Despite the immense difficulties, during the 10 years of its existence the State of Israel has achieved remarkable results in the various fields of health, which are reflected in the country's vital statistics. The birth rate is high (28) but the death rate low (6.3); infant mortality at 32 is only a fraction of that in most countries in the Middle East; life expectancy (68) is comparable with that in the U.S.A. (72), and the mortality rate from tuberculosis (7.1) is the second lowest in the world.

There was a symposium on blood diseases. Dr. Y. MATOTH said a high incidence of thalassaemia had been found among Jews from Kurdistan. Over a five-year period 80 new cases of thalassaemia had been diagnosed among Kurdish children and adults in the Jerusalem area, including 11 new cases of thalassaemia major, the homozygous state. The frequency of thalassaemia in this Kurdish population had been calculated as 0.0663 for the homozygous state and 0.123 for the heterozygous state. Rare instances of thalassaemia had been encountered among Jews from other Middle Eastern regions, but an extensive search for abnormal haemoglobins by paper electrophoresis among members of various other Jewish communities had yielded negative results. It seemed, therefore, that thalassaemia was the only haemoglobinopathy affecting Jews in Israel, and that it was virtually limited to those from Kurdistan. Dr. C. SHEBA said that haemolytic reactions to sulpha drugs and other noxious agents occurred only among the non-European Jews. The erythrocytes of those who had suffered from such reactions showed a low glutathione concentration, glutathione instability, defective glucose-6-phosphate-dihydrogenase activity, and a low rate of incorporation of radioactive glycine into glutathione. In a survey of 2,000 control subjects, no such abnormalities were found among European Jews, while 10% of the non-European Jews were affected. The abnormality was most frequent among those originating from Iraq (about 20%); in other groups studied (Yemenites or immigrants from North Africa) the frequency was about 5%. In Italy this trait is found only in subjects of Sardinian and Sicilian origin. Genetic evaluation showed the abnormal trait to be sex-linked, incompletely dominant, with sex-conditioned variable expressivity.

Dr. D. BRUNER spoke on myocardial infarction in Yemenite Jews. Conditions in Israel presented an excellent opportunity for studying the aetiology of atherosclerotic heart disease and the relationship between lipid patterns and the incidence of coronary disease. The very large immigrant population of European Jews had a high incidence of coronary disease as in the Western world, while the Yemenite Jews were practically free from atherosclerotic heart disease and angina pectoris in middle age. An analysis of the various lipid fractions in 74 patients with myocardial infarction showed that in only 10.8% of them was the β-cholesterol level less than 180 mg./100 ml. On the other hand none of 32 Yemenite farmers had a β-cholesterol level over 180. Despite a low total cholesterol among the Yemenites, α-cholesterol levels were very similar in both the European (healthy and affected) and the Yemenite groups studied.

Dr. E. E. LIEBER (Great Britain) described an inquiry into whether certain industrial dusts and vapours in a factory could cause chest disease. The dusts contained glass monofilaments, beryllium-copper alloy, epoxy resins, and polyesters. He regarded the occasional case of emphysema as the result of the action of polyester and epoxy resin dusts on the pulmonary neurovascular tissue. Lung markings caused by polyester dust were due purely to its mechanical irritant effect, not to any chemical toxic reaction. The prognosis in all cases was excellent, and the patient's condition did not continue to deteriorate after removal from exposure. Normal dust extraction equipment plus the usual additional prophylactic measures were adequate to protect workers engaged in handling glass fibres or epoxy resins in any form.

Professor A. DE VRIES gave the results of an epidemiological investigation of urolithiasis in Israel. In 12 settlements, selected because of different climate and ethnic composition, the incidence was high. In males the incidence was 14.4% and in females 8.8%. The incidence was highest in the hottest and lowest in the coolest regions, higher in immigrants from Europe than in those from the Middle East and North Africa, low in those born in Israel and in immigrants below the age of 18, though in the latter it rose sharply after that age. In the large majority of the patients the urolithiasis developed within the first five years of arrival in Israel. Inadequate fluid intake was the most satisfactory explanation of these findings. Ethnic differences could be explained by differences in drinking habits.

PROMOTION OF THE SALE OF DRUGS

AMERICAN CODE

The two main associations of drug manufacturers in the U.S.A.—the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association—have recently merged. The newly formed organization is called the Pharmaceutical Manufacturers' Association, and one of its first actions was to issue the following statement of principles[1] applying to the promotion of pharmaceutical products sold only to the medical and allied professions:

"We, members of the Pharmaceutical Manufacturers' Association, recognizing our responsibilities and obligations to promote the public welfare and to maintain honourable, fair and friendly relations with the medical profession, with associated sciences, and with the public, do pledge ourselves to the following statement of principles:

"(1) Prompt, complete, conservative and accurate information concerning therapeutic agents shall be made available to the medical profession.

"(2) Any statement involved in product promotional communications must be supported by adequate and acceptable scientific evidence. Claims must not be stronger than such evidence warrants. Every effort must be made to avoid ambiguity and implied endorsement. Whenever market, statistical, or background information or references to unpublished literature or observations are used in promotional literature, the source must be available to the physician upon request.

"(3) Quotations from the medical literature or from the personal communications of clinical investigators in promotional communications must not change or distort the true meaning of the author.

"(4) If it is necessary to include comparisons of drugs in promotional communications, such comparisons must be

[1] *Drug Trade News*, June 2, 1958.

used only when they are constructive to the physician and made on a sound, professional and factual basis. Trademarks are private property that can be used legally only by or with the consent of owners of trademarks.

"(5) The release to the lay public of information on the clinical use of a new drug or to a new use of an established drug prior to adequate acceptance and presentation to the medical profession is not in the best interests of the medical profession or the layman.

"(6) All medical claims and assertions contained in promotional communications should have medical review prior to their release.

"(7) Any violation of these principles brought to the attention of the president of the Pharmaceutical Manufacturers' Association shall be referred by him to the Board of Directors."

MEDICAL DEFENCE UNION

The 73rd annual meeting of the Medical Defence Union was held this year at the Royal Victoria Infirmary, Newcastle upon Tyne. It took place on September 16, under the chairmanship of Dr. S. COCHRANE SHANKS, president of the Union, who presented the annual report. The total membership at July 15 was 45,374, of whom 8,182 were women and 3,258 life members. During 1957 the Union handled 2,492 cases, compared with 2,379 the year before. The accounts, which were presented by Dr. HENRY ROBINSON, showed an adverse balance of £19,241, owing to generally rising costs and the rise in indemnity claims (over £33,000). The subscription had had to be raised on May 1 from £2 to £3 per annum, but this sum was eligible for tax relief under the Finance Act, 1958, as a necessary expense, making the net amount now no more than 34s. 6d.

Hazards of Practice

Mr. A. HEDLEY WHYTE, senior surgeon to the Royal Victoria Infirmary, gave the customary address, choosing as his subject for his largely student audience "The Hazards of Practice." After relating a number of the commoner disasters and one unusual one in which recently a pathologist was asked to examine a specimen of duodenum obtained by sigmoidoscopy, Mr. Hedley Whyte described some of the precautions currently in force at the Infirmary. In particular he described the rigorous safeguards adopted routinely against any chance of the surgeon operating on the wrong patient, or a wrong part of him, of swabs or other objects being left behind in body cavities, of incompatible blood transfusion, and against tetanus.

In the theatre three kinds of swab were used—packs, mops, and stamp gauzes. Stamp gauzes were always on holders and never loose. Packs and mops were of the "raytex" variety, marked with a thin radio-opaque line. These swabs were counted, before sterilization, into bundles tied in fives, counted out again before operation, and the number in use chalked on a board for all to see. Before the beginning of wound closure the swab count, clip and needle counts, must all be correct, and similarly a second correct count must be agreed before the patient left the theatre. They thought this the best method, and had no use for tapes or similar contraptions tied to swabs.

The problem of tetanus was not so satisfactory, although the outcome was less gloomy than heretofore. Cases still occurred, however, at the rate of two or three a year. At the Royal Victoria Infirmary all patients were given some sort of prophylactic treatment, irrespective of the site of the wound, whether or not it was penetrating, or the likelihood of its being contaminated. No case was missed, so vigilant was this service. Usually the patient was given a divided dose of 1,500 units of A.T.S. in 1 ml. First the patient was questioned about his susceptibility to various foods and about asthma or hay-fever, and then given 0.2 ml. of A.T.S., and after 20 minutes the remaining 0.8 ml. If there was any possibility of sensitivity, then a minute intradermal dose was tried, and if there was no untoward reaction then the

(*Continued at foot of next column*)

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Uniplex (Weddel Pharmaceuticals, Division of the Union International Co. Ltd.). Each tablet contains 125 mg. of granulated whole liver extract, 1 mg. aneurine hydrochloride, 1 mg. riboflavine, and 5 mg. nicotinamide. Uniplex is intended for treating such conditions as pyrexia, debility, neuritis, glossitis, diabetes, pregnancy, lactation, or impaired function of kidney or liver in which the intake of vitamin B may be below normal.

Deficiency symptoms of vitamin-B complex vary considerably, since it is concerned with general metabolism, and all types of tissue may be affected. When symptoms are due to a deficiency of it, a satisfactory response may be expected on administration of this preparation. Patients who have to live on a restricted diet may also be helped by this product.

N.H.S. basic price: 50 tabs., 2s. 8d.

Ferronicum (Sandoz Products Ltd.).—Each sugar-coated tablet contains ferrous gluconate 300 mg., equivalent to 35 mg. bivalent elemental iron. This preparation is intended for the treatment of iron-deficiency anaemia in doses of 2 tablets three times daily in post-haemorrhagic anaemia, 3–4 tablets three times daily in essential hypochromic anaemia, and for anaemia after gastric resection 4 tablets five times daily; for children up to 12 months 1–2 tablets daily crushed in water, and for older children 3–9 tablets daily. A normal response should be obtained with 3–6 tablets daily. While this is an effective preparation in the treatment of iron-deficiency anaemia, it costs more than ferrous gluconate tablets *N.F.*, which have the same clinical effects.

N.H.S. basic price: 100 tabs., 3s.

Distivit Vitamin B_{12} Peptide Complex (The Distillers Co. (Biochemicals) Ltd.).—A tablet contains cyanocobalamin (vitamin B_{12}) combined with a peptide to form what is called vitamin B_{12} peptide complex. Supplied in tablets containing 20 or 100 μg. vitamin B_{12}. This is intended for the oral treatment of pernicious anaemia and similar megaloblastic anaemias as well as subacute combined degeneration of the cord. The treatment recommended is 100 μg. of B_{12} in the form of this complex three times daily for ten days, followed by 100 μg. daily until the blood count reaches normal levels. Maintenance dose thereafter is adjusted according to the response obtained in the patient.

This is a new preparation, and the follow-up of patients treated with it for pernicious anaemia is not yet adequate to judge its effects fully. A few cases have been reported and have been treated over short periods of time with good results, but other patients have not responded so well. Long-term observations are needed before a full assessment can be made of the value of this treatment in pernicious anaemia, and it would be worth making these.

N.H.S. basic price: 20-μg. tabs., 100 for 8s. 8d.; 100-μg. tabs., 100 for 21s. 10d.

(*Continued from preceding column*)

remainder was given in 20 minutes. Should a reaction be feared, then toxoid was administered, a second dose being given in two weeks' time. Where it could be ascertained that triple vaccine against diphtheria, whooping-cough, and tetanus had been given in childhood, as was increasingly the case, then a 1 ml. dose of toxoid only was given. During the last five years they had had 14 cases of tetanus, of which seven recovered, although the last two cases had died. It was disturbing that both these last two cases had been treated prophylactically before admission, one at home and the other at another hospital, and both with apparently adequate dosage.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Medical Education

SIR,—I very much welcomed the article of Dr. Richard Scott (*Journal*, September 6, p. 577) and the report of the College of General Practitioners on psychological medicine (p. 585) in your educational number. I ask myself whether the recommendations made therein are good, and also what response the medical schools should make. Progress in medical education occurs slowly because it is generally envisaged in a fixed framework; the effort to find more room for more subjects is frustrated by the difficulties of omitting or contracting others. There would soon be no progress at all were it not that a less rigid curriculum has increased teaching freedom, and were it not that the faint possibility of change in examination method gives some hope that the mutual neurosis of students and teachers (comparable to the situation of 11-plus) might be eased.

The demands made in these two articles are, firstly from Dr. Scott, that students should see general practice for two weeks at a late date in their training, and after his analysis of the defects of medical teaching in hospitals the conclusion is to me *ridiculus mus*. The College of General Practitioners' report requires greater emphasis on normal psychology and psychological medicine, a compulsory question on these subjects in the final examination (I view with deep fear and depression: "What are the indications for E.C.T.?"), but, fearing the inadequacy of these suggestions, a demand also for more postgraduate education. I am full of sympathy, but think that these demands should be much more radical and courageous. If, as Dr. Scott says, the diagnostic method of the general practitioner involves a synthesis of all factors, whereas the hospital method is analytical and exclusive of data, then if the former is right the latter should be brought into line. If, as the College suggests, 30% of all morbidity seen by practitioners is due to mental stress, etc., then too we must adapt our teaching to meet this.

We will fail to correct our teaching until we recognize that medicine must be a study of all aspects of man as he lives in society. Social medicine, psychological medicine, or organic medicine are all useful but misleading isolates from the whole complex, and each tends by itself to give a distorted view. Six years are spent in undergraduate medical education; for two and a half to three years Man is cut into pieces in studies of anatomy, physiology, and biochemistry, and towards the end of the period there may be some lectures on man's behaviour. These isolates are never integrated, and Man (*Homo sapiens*—such is our conceit) has been dissected with a scalpel, microscope, a chemical balance, etc. The student, thinking that when he enters his clinical years he will meet people, comes up against an introductory course which should tell him that all these dull things he has learnt and is trying so hard to forget are his basic sciences, and the process of integration which should commence is progressively swamped by fact-cramming—but of course he is considered to be too immature for psychological medicine. The eclectic psychiatrists sometimes pooh-pooh the Id and the Ego and the Freudian heresy, and belabour the student with taxonomy, fear of transference situations (our old friend the doctor–patient relationship). Why can't the student be taught about his own mental maturation, his own adjustment to society from birth onward, so that he himself can mature more rapidly and become a real doctor?

It is a pity that the term "psychosomatic" is so useful for a limited group of disorders, for indeed all medicine is psychosomatic and each individual's psyche develops in his ever-changing social setting. Can we not *begin* our clinical studies with this in mind? Many physicians have found insufficient help from their psychiatric colleagues in their everyday work; they envy their American colleagues who have fully staffed psychotherapy departments available. So they are now forced, perhaps fortunately, to learn about this large aspect of their patients. Can we not now teach our students from the commencement of their clinical work that a case history is not a record of symptoms, plus a few isolated data about family and social setting, but a history of a person and how it is to be understood? Let the student find out why Mr. A. visits the pub and puts off his evening return to his termagant wife, find out why Mrs. A *is* a termagant wife; and to understand why Mrs. B. is ill, she being a rejected but still matriarchal mother-in-law; why Mr. C., middle-aged, is unmarried, hypertensive, and still living with his parents. If such is the setting of so much illness (*vide* H. G. Wolff, *Lancet*, 1958, **2**, 206) much of the teaching should be done by the physician, who will need help, but the important thing is to keep the student in this human atmosphere for eighteen months in medical, surgical, paediatric, and gynaecological departments only: the surgeon too must teach him about people, their fears of pain and surgery, the loss of employment, the full meaning of rehabilitation; the paediatrician must teach about mothers and fathers, affection, security, and the lack of these; the gynaecologist must teach about women, and that if menstrual upsets are caused by stress psychological methods should be used, teach too what a womb means to a woman and what threatened womblessness portends. Of course the student must learn too that estimations of electrolytes, surgical procedures, isotopes, etc., are also instruments for the investigation of or treatment of a sick human being. Quite early he must learn to talk to patients—learn what to say and ask, learn how to listen with every faculty alert, and to interpret the verbal and other communications with patients, understand too what people feel like when distended with barium enemas in dark rooms, or sigmoidoscoped with bottoms exposed. What shocking examples so many of us set in our rounds, how little we know what a frantic hour ward sisters spend soothing patients, answering their questions—What did HE say? What did HE mean? The busy teaching physician must educate his staff because the eager registrar is often cynical behind his back; perhaps they should not be promoted until they have had a dose of Dr. Balint or a near equivalent from some of his enthusiastic pupils who have been so actively spreading the light.

I have only sketched an approach. I have said nothing new, there is much agreement, but the working out is very urgent before the distended curriculum bursts.—I am, etc.,

London, W.1. HUGH GAINSBOROUGH.

SIR,—The educational number of the *Journal* (September 6) and the report of the College of General Practitioners' working party on psychological medicine in general practice (*Journal*, September 6, p. 585) raise important issues.

Pre-registration Training.—I believe that this is unnecessarily protracted by one year by virtue of an over-academic preclinical course. To give but one example, 18 months are spent learning anatomy in fine detail, soon to be forgotten. The acquisition of such knowledge is the concern of the postgraduate budding anatomist or surgeon, etc. The fundamentals, which can be learnt in half the time, are adequate for the general practitioner. During clinical training, emphasis is still centred on disease *per se*. The revelation now to me is that what matters more is the patient's mental manipulation of his disease and environment—including his medical advisers—and the varying degree of ego breakdown, with its concomitant somatic effects, in different persons affected by a similar aetiological agent. In addition to teaching normal and abnormal psychology as such, their participation in every branch of medicine must be impressed upon students, so that from the outset they have a deeper insight into their patients' problems. Now that at least a third of disease has been assigned to the realm of psychopathology, the suggested inclusion of one compulsory psychiatric question in finals (marked, we hope, by the "interested" examiner) is conservatively timid. There should of course be both a written and an oral examination. The introduction of the pre-registration year, to be served in hospital, is an impertinence to the qualified doctor. It serves no extrinsic value and should be abolished.

Post-registration Study.—The plea for improved training facilities for the general practitioner is well founded. Part-time courses with adequate instruction for higher qualifications in all branches are also necessary. Lack of available time and lack of pecuniary reward for doing specialized work in the N.H.S. are difficulties which could be met by a reduction in list size with commensurate financial compensation.

I disagree with the working party's opinion that the use of hypnotism is, "at present, outside the normal province of general practice." I find it of real value. For example, when symptom-removal by direct suggestion is employed, say in so-called psychogenic rheumatism, it compares favourably with the hospital physiotherapy department as a faith-healing agent, and time, expense, and manpower are saved. Although much is unknown about hypnosis, the fact remains that its lay use is increasing. Rather than dismiss it arbitrarily, the wise course would be to establish a university department for its scientific study and appraisal.

In the National Health Service of the future the role of the general practitioner will increasingly become that of an intermediary whose duties could be largely performed by a civil servant, unless the doctor is given the opportunity to establish his legitimate position as a person of education and authority in that particular branch of general practice in which he has special interest.—I am, etc.,

Edmonton, N.9. HAROLD FOX.

Contraception by Inhibition of Ovulation

SIR,—Dr. B. H. Kirman (*Journal*, August 30, p. 565) criticizes your annotation (*Journal*, August 2, p. 297) on the use of "enavid" as an oral contraceptive. His criticisms are based on several misconceptions. Firstly, he compares the toxicity of progesterone, a naturally occurring hormone, with that of aminopterin, a known tissue poison, whose effect upon fertility may well include an abortifacient action mediated by its toxic effect upon the foetus. It is quite misleading to compare the toxic action of aminopterin with the very occasional report of foetal abnormalities following progesterone and other progestational agents. In any case his fears are, I believe, groundless, as the design of the Puerto Rican study is such that any patient becoming pregnant would automatically discontinue taking the tablets, and not therefore be exposed to the hypothetical risk to the foetus which might result from continued hormone administration during the early months of pregnancy. Quite apart from this consideration, I would like to point out that foetal malformation has not so far been reported following administration of enavid in pregnancy. (There is a growing experience of such administration in the treatment of recurrent abortion, for which the use of a progestational agent has been suggested by Goldzieher and Benigno.[1]) The intrinsic oestrogenic activity of enavid encourages the hope that this drug may prove safer for administration during pregnancy than other progestational agents, many of which, including progesterone itself, show slight androgenic activity in some situations.

Secondly, Dr. Kirman comments that "it is surely unwise to permit the marketing and widespread use of such potent compounds for this purpose" (contraception). If Dr. Kirman is under the impression that enavid is marketed for this purpose, he is under a misapprehension, as this is not the case. The makers have at no time made such a recommendation for its use. In due course the field trial in Puerto Rico will show whether or not long-term use of this method of contraception is safe. Thirdly, Dr. Kirman criticizes the choice of Puerto Rico for the site of the trial. The choice was in fact a good one for several reasons. The population problem in Puerto Rico is such that there is a strongly felt need for a reliable method of contraception. There was already a useful background knowledge of the fertility of the population to be studied. The fact that the previous pregnancy rate was a high one rendered the population particularly suitable for this type of field trial.

I would agree entirely with your annotation that even at this early stage (third year) of a long-term scientific study "a remarkable step forward" has been made.—I am, etc.,

High Wycombe, Bucks. G. R. VENNING, Medical Director, G. D. Searle & Co. Ltd.

REFERENCE

[1] Goldzieher, J. W., and Benigno, B. B., *Amer. J. Obstet. Gynec.*, 1958, 75, 1202.

Anaesthetic Hazards

SIR,—The occupational hazards of an anaesthetist include those of drug addiction, unhappily more common, I believe, than generally recognized. Adopting the methods recommended by Dr. Victor Goldman (*Journal*, August 2, p. 327) of not only smelling, not only sniffing, but testing by the administrator everything it is intended to use on the patient, would seem to add greatly to the risks referred to above. Addiction to nitrous oxide/oxygen, nitrous oxide/air, not to mention the more potent inhalational agents, would seem to be encouraged by this. Surely safety is ensured by careful checking of cylinders, connexions, and bottle contents.—I am, etc.,

Plymouth. R. E. ANGEL.

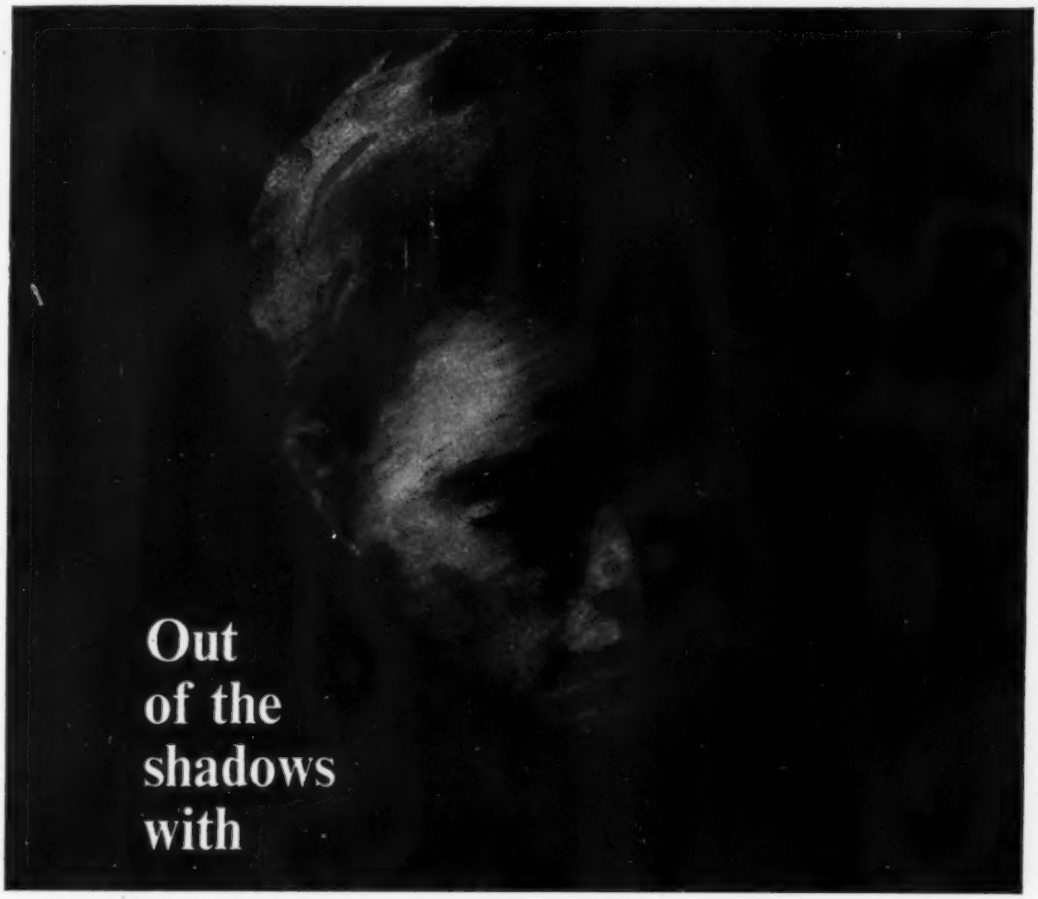
Antenatal Irradiation and Childhood Malignancies

SIR,—The fact that the authors of the investigation into childhood malignancies[1] have now stated that antenatal *x*-rays cannot account for the apparent rise in infantile cancer will be welcomed by all *x*-ray workers. This conclusion does not, however, go far enough in dispelling the impression created and spread by the lay press that diagnostic *x*-ray examinations are dangerous and harmful. The investigators themselves are convinced that they proved beyond all reasonable doubt that there exists a causal relationship between antenatal diagnostic irradiation and malignancy, and in this they seem to be supported by an irrefutable set of figures. If their results were accepted it would mean that one child of every 3,000 mothers who had a pregnancy *x*-ray would develop cancer and that between 20 and 30 cases of childhood cancer out of a total of 500 cases a year might be directly attributable to antenatal irradiation.

The publication of their preliminary report[2] has resulted in antenatal *x*-ray examinations being severely curtailed by obstetricians and radiologists. It can only be a guess that the lack of *x*-ray confirmation of various maternal or foetal conditions may maintain the high maternal death rate (399 in 1956), the stillbirth rate (16,505), and the neonatal death rate (11,779). If one assumes that with adequate *x*-ray surveys of the pregnant population only as little as 1% of these mothers and babies could be saved, this would give us over 10 times as many live births as dead babies from a possible malignancy in childhood, not to mention fewer feeble-minded and spastic children following birth injuries. In spite of the apparent smallness of the risk attached to such examinations, I still feel it necessary to remove the stigma which has been attached to such *x*-ray procedures for the past two years since the publication of the preliminary report.

I analysed the figures of my own *x*-ray examinations on pregnant women during the past 15 years and found among 4,000 cases *x*-rayed in one hospital in Hertfordshire no case of childhood leukaemia, but there were six cases of leukaemia in children of non-irradiated mothers. A rough check on a further 3,000 cases from a London maternity hospital did not reveal a post-radiation leukaemia either. I am fully aware that my own figures are not statistically important, but they still suggest that the problem should be critically re-examined in case there is a flaw in the investigations which in itself would account for the unusual and unexpected result of their survey.

In my opinion the authors[1] have not paid enough attention to the various groups of maternal characteristics which differ widely in their respective numbers in the case and control groups and which may constitute an increased indication for the taking of radiographs. The authors set out to prove that a certain factor had been induced in the foetus during intrauterine life which would eventually develop into a malignant condition. Therefore not only the children but also the maternal state before and during pregnancy should have been closely matched in the two groups. The total differences in numbers of irradiated women between the case and control groups (their Table VII) amounts to 60 for a three-year period. If it can be proved that these 60 cases can be accounted for by differences in the two



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groups of mothers, then the results of this survey would become very questionable.

(1) Primigravidae in the survey amounted to 510 in the case group, against only 427 controls with 8.4% of the latter *x*-rayed. The rate of multiparae (with at least two previous births) *x*-rayed is given as 6.8%. But such a percentage difference cannot occur in a normal control group, as every *x*-ray department will examine at least twice as many primigravidae as multiparae. (My own figures: 1957, 2.6 : 1; 1958, so far, as 2.5 : 1). The only explanation for the authors' ratio (8.4% : 6.8% = 1.2 : 1) can lie in considerable under-reporting of the controls—i.e., one mother in 40 failed to record an antenatal *x*-ray. If we assume that the percentage of primigravidae *x*-rayed was twice that of multiparae, then we arrive at 13.6% for 510 primigravidae = 69 cases. This would give 33 more cases than those recorded, and it would reduce the differential between the case and control group to less than 30.

(2) Elderly mothers are much more frequently *x*-rayed than a young mother. I believe that there were a total of 67 women over 40 years in the case group, and, in the absence of figures supplied, I assume that over 30 of these were surplus over the control group.

(3) Mothers' illnesses during pregnancy fall into two groups: (*a*) *Infectious diseases*, of which an excess of 12 was found in the neoplastic group, and (*b*) *diseases specifically associated with pregnancy*: toxaemias, genito-urinary infections, and threatened abortions, which showed a surplus of 36 on the case side. It is obvious that if 48 extra cases of similar illnesses were included on the control side then the number of *x*-ray cases would go up considerably in this group.

(4) Mothers' past histories disclose an excess of 37 case mothers with a total of 48 abortions and a further seven case mothers with a history of at least one stillborn child. Here again the clinician will order more *x*-ray examinations than in a group of normal patients.

Altogether the last three groups show an excess of 122 anomalous mothers in the case group, each one of whom is a more likely subject for an *x*-ray examination than a normal pregnancy case. If a corresponding number of 122 abnormal women were included on the control side with the object of making both groups reasonably equal then we could expect that at least one in four of these anomalous types would be referred for an *x*-ray examination. This would reduce the difference between the two groups to zero and would have the following results: (1) The whole argument that antenatal *x*-rays in small doses can be responsible for childhood malignancies becomes null and void. (2) It would throw doubt upon the widely held belief that human foetal cells are more susceptible to *x*-radiation than adult cells. (3) It would confirm the view that a fairly high threshold dose exists below which *x*-rays are harmless.—I am, etc.,

London, W.1. J. RABINOWITCH.

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Sweet Tooth and Decay

SIR,—In your issue of September 6 (p. 638) is printed a letter by Mr. F. T. Ranson that calls for early reply. He argues that sugar does not seem likely to be the cause of dental decay, since the chewing of sugar-cane in Jamaica appears to be a powerful preventer of decay. After three years in Trinidad during the war I would accept the latter fact without hesitation, but the reason is that sugar-cane is a natural material. Not only is the fibre in the sugar-cane as great a cleanser of the teeth as any in existence, but in addition any cane cells left lying around the teeth afterwards are still alive and so the antibodies in these cells prevent bacteria attacking them, just as our own do as long as we are alive. In both these respects the unnatural sweetmeats and other contents of confectionery shops present a most striking and tragic contrast.—I am, etc.,

Gosport, Hants. T. L. CLEAVE.

SIR,—Having read your article "Sweet Tooth and Decay" (*Journal*, August 2, p. 293) and the interesting point raised later by Mr. F. T. Ranson (*Journal*, September 6, p. 638) that "chewing sugar-cane and good teeth go together," may I say that there is some truth in that statement? The fact is that it is not only due to sugar-cane that the West Indians have such excellent teeth—not forgetting the sunshine for a moment—it is the chewing of hard food that gives exercise to the muscles of the jaw, thereby promoting better circulation, consequently denser calcification and dentition and glossy enamelling. We must not forget that Asiatics and African races not only avoid soft sloppy feeding but clean their teeth with religious scruple, not leaving any bacteria to flourish and cause havoc. Medical men and especially dental surgeons hope that the habit of oral hygiene will be inculcated in schoolchildren all over the world.—I am, etc.,

Abbots Langley, Herts. A. K. K. NYAZAI.

Fishbone Furunculosis

SIR,—During the late summer months at Lowestoft and Llandudno I have seen a number of cases of a skin eruption which occurs amongst fishermen. Following a fishbone scratch (apparently irrespective of the type of fish) small furuncles crop up on the fingers. They resemble normal furuncles but are not so painful and there is no lymphadenopathy. *Staphylococcus aureus* has been grown from the yellow discharge. The condition rapidly responds to intramuscular penicillin. The local fishermen say the condition is common amongst them, but only during the months of August and September. I would be interested to hear of any further cases.—I am, etc.,

Llandudno. PETER COOK.

Premonition of Death

SIR,—On paying my usual routine visit one Tuesday afternoon to a male patient of mine dying from cancer of the lung, the patient took hold of my hands, thanked me for all my attention, and then proceeded to tell me that I would not need to call and see him after Thursday, as he was going to die at 2.30 that afternoon. Needless to say, I comforted him the best way I could, told him to exclude such thoughts from his mind, and promised to look in again.

On late Thursday afternoon I received a message from a member of his family that their father had passed away peacefully. A few days later two daughters of the deceased came to consult me, and in the course of our conversation told me that the day before their father died he had summoned all the members of the family together and repeated to them what he had told me—namely, that he would die the following day at 2.30. On the predicted day, all the members of his family were with him in his bedroom except his wife. As 2.30 was approaching he urgently called for his wife to come in, saying, "Hurry, hurry, before it is too late." She came running into the room, and on the stroke of 2.30, according to the two daughters, "He sighed, raised both hands behind his head, smiled, and passed away." I wonder if any of my colleagues have had a similar experience.—I am, etc.,

Glasgow, S.W.3. ARNOLD B. COWAN.

Human Factor in Diagnosis

SIR,—I found the article by Dr. C. P. E. Elliott-Binns on the human factor as a cause of delay in diagnosis in general practice (*Journal*, August 2, p. 271) very interesting. I am sure every general practitioner who has been in practice for some time will say to himself after reading it, "Well, I am not the only one who has missed a diagnosis." I think the following type of case is common enough and comes within the third criterion that Dr. Elliott-Binns mentions. In this particular type of case the doctor, after a thorough examination, knows there is something wrong but cannot find the cause. He refers the patient to hospital, where he is investigated as an in- or out-patient, a diagnosis is made, treatment suggested or carried out, and the patient is sent home. Somehow the general practitioner is not happy about the patient's progress, and there are further admissions or attendances at the hospital. The

doctor is none the wiser and begins to think that the patient is either a hypochondriac or a hysteric. Then something turns up and to his horror the doctor finds his patient is suffering from an inoperable condition which is going to prove fatal.

In my view these types of case are here to stay, no matter what one does. But the moral of them surely is that reference of a patient to hospital does not entirely absolve the general practitioner from diagnostic responsibility nor does it relieve his mind from worry when he views the case in retrospect.—I am, etc..

Liverpool, 18. H. J. PRATAP.

SIR,—I have been very interested by the article by Dr. C. P. E. Elliott-Binns (*Journal*, August 2, p. 271) and the letter from Dr. M. H. S. Bound (*Journal*, August 23, p. 512) on the human factor in diagnosis. Any doctor of experience can bear out how unpleasant, not to say sometimes fatal, results are due to this factor. They are the recognized penalties of snap diagnosis, and such events, as pointed out, may well inculcate a spirit of humility. While we bewail our insufficiency, however, may we not take comfort from the fact that the number of such accidents and fatalities fades into insignificance when compared with those originating from the same factor in industry and on the roads. On the credit side, also, must be placed the many happy hits of snap diagnosis. Most of us can recall moments when a sort of second sight came to our aid. This, too, may surely be regarded as a human factor, and one which contributes not seldom to important scientific discovery as well as helping to lighten and brighten the multiform perplexities of our profession.—I am, etc.,

Bristol. P. T. MACDONALD.

Cord Round the Neck

SIR,—The cases from the literature of multiple loops of umbilical cord around the neck quoted by Dr. H. E. Reiss (*Journal*, June 14, p. 1394) recalled to my mind a case I attended in 1955. As there appears to be no comparable case among those he has quoted, I considered that this information is worth recording. The patient was a primigravida who came into labour at term. A male child weighing 6 lb. 8 oz. (3 kg.) presented with six loops of cord around the neck. The loops were easily removed over the head without cutting, and at no stage was there any evidence of foetal distress. The length of the cord was not measured, but it was, of course, extremely long.—I am, etc.,

Hamilton, New Zealand. R. E. WRIGHT-ST. CLAIR.

Cancer Education

SIR,—I was interested and slightly amused to see that your correspondent Dr. J. Kenworthy Ogden (*Journal*, August 9, p. 389) has resurrected that old controversy concerning the definition of cure in malignant disease. Everybody will agree with him that in order to produce scientific proof of cure a post-mortem examination must be carried out, but not only is it necessary to find evidence of a different cause of death but it is essential to cut and scrutinize serial sections one cell thick from the scalp to the soles of the feet, a somewhat lengthy undertaking. The same is true for tuberculosis to discover a live tubercle bacillus, and many other diseases. In practice the yardstick of five years' survival without signs or symptoms is very useful.

Dr. Ogden then says it is unwise to instil in the minds of the public that some cancers are "curable" if treated in an early stage, but it is true from the patients' point of view if they get rid of the symptoms and signs and possibly live another twenty years. They are unlikely to worry if a few malignant cells are found post mortem.

Space does not permit me to discuss cancer statistics on which your correspondent touches. He goes on to say he does not object to the public receiving cancer education provided it is based on truth. Truth depends on two people, the person who utters the words, and the person who hears them. There is no easier way of telling a lie than by telling the exact scientific truth to a lay person who has no scientific training. I wonder what your correspondent would like us to say to the public. Possibly we should say, "If you get cancer you are bound to die even if it is only discovered post mortem many years later." What value would this be to the lay person? The objects of cancer education are to relieve the minds of thousands of people from fear of the disease, and to obtain some more early stage diagnosis, by putting before them a true picture of what can happen if certain cancers (particularly the accessible cancers) are treated in an "early stage." Everybody realizes that the prognosis depends largely on the degree of malignancy of the particular tumour, but unless we revise our ideas about cancer being a progressive disease nobody will deny that the earlier the stage of the disease when the patient is treated the better the prospect of saving life.—I am, etc.,

Oxford. MALCOLM DONALDSON.

Adrenalectomy and Hypertension

SIR,—Your admirable annotation on "adrenalectomy and hypertension" (*Journal*, August 30, p. 555) could only be criticized as being a little too discouraging about the operation of total adrenalectomy for the malignant phase. If the cardiologists refer such cases for surgery after renal failure has become established the mortality will be prohibitive. However, there are many cases of malignant hypertension which are not yet in renal failure, and if such cases were operated upon as soon as the blood urea, etc., commences to rise the results could be most satisfactory. The blood pressure *per se* is unlikely to be reduced to any marked degree, but the eye changes and the congestive heart changes will be relieved, while the patient's general comfort will be greatly increased.[1] If we exclude the 5 cases of failing renal function from our own series of 13 operations[2] we are left with 8 patients, all of whom are alive, 1 at six years,[3] 3 at four years, 2 at three years, and 2 at over two years. It is interesting that no further deaths have occurred after the second year.—I am, etc.,

London, W.1. HOWARD G. HANLEY.

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Aetiology of Coronary Disease

SIR,—I read with great interest the article by Professor R. P. Malhotra and Dr. N. S. Pathania on coronary heart disease in their part of India (*Journal*, August 30, p. 528). It is a valuable contribution to our understanding of the disease and I hope may encourage others in India to carry out similar surveys on the differential incidence of disease according to geography and racial habits in that country.

That there is a profound difference in the incidence of the common "Western" diseases of stress, so-called, in different parts of the Indo-Pakistan subcontinent has been very evident for some time. My own field of work has been in East Pakistan and North-east India over 10 years, and I have been intrigued by the difference in incidence, between the north-east and north-west areas of the subcontinent, of the two large disease groups, hypertension and peptic ulcer. Amongst Bengalis, hypertension, and in particular malignant hypertension, seems to be relatively common, though the incidence of the arteriosclerotic conditions fairly rare. Valvular heart disease caused by either rheumatic fever or syphilis is common, but coronary heart disease extremely rare. I cannot recall seeing a single patient complaining of angina of effort, but do remember two cases of coronary thrombosis, both in Muslims of the upper income group, both West Pakistanis, native of an area adjacent to Professor Malhotra's. On the other hand, obliterative arterial disease of the Buerger type is fairly common. It would have been helpful if Professor Malhotra had subdivided his cases in religious groups, as the Sikhs and Hindus have, as he states, differing customs regarding smoking and alcohol, and some difference may have been detected.

I wonder, from his findings and in the light of my own experience, what are the varying influences of diet and mental stress in coronary disease. The Punjabi and Bengali diets differ mainly in the Bengali being a rice-eater while the Punjabi is a wheat-eater.

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REFERENCES:
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Apart from that, diet varies according to income and religion. Muslims tend to be meat-eaters to a greater extent than Hindus, many of whom are vegetarians, but a greater amount of fish is eaten than in the West. The main oil used for cooking is mustard oil. Obesity is probably just as common as in the Punjab, but appears to have no relation to causation in our area. I doubt very much if the differences in types of oils used in the two areas can have an influence, but it would perhaps be wise to eliminate this by an analytical study of the various Indian oils before we dismiss the cholesterol content as being irrelevant.

The occupation of the person and his social status may play a very important part. My work was mainly amongst the poorer groups of the population, and it is possible that there may be a higher incidence in Bengali upper-class groups than I have been aware of. However, I do not think that that factor alone is sufficient to account for such a great difference in incidence in the two areas.

Comparisons with colleagues in other parts of Bengal and Assam seem to indicate that the incidence of coronary disease in that area is indeed much lower than in Professor Malhotra's area. What is the answer? I think that the badly neglected study of the epidemiology of diseases such as coronary disease and peptic ulcer in India and Pakistan may throw a great deal of fresh light on these two still very enigmatic "stress" diseases. Diet, customs, and ways of life need to be studied in mass surveys such as have been carried out here in relation to lung carcinoma. Everyone who has lived in India and Pakistan for any length of time knows that the Bengali is by no means a less emotional man than the Punjabi. Why should he not be subject to coronary disease yet be plagued by peptic ulcer?—I am, etc.,

Eastbourne. I. T. PATRICK.

Halothane Concentration

SIR,—We have followed with great interest the correspondence in your columns on halothane concentration and hope that a view in perspective on this important problem might not be amiss. Our use of the Rowbotham's bottle in a circle absorber was part of a phased plan to demonstrate the safety and economy of vaporizing halothane in a circle system; this particular phase is now over,[1 2] and it was never denied that the use of the bottle or indeed any vaporizer for this purpose offered some slight resistance to inspiration. Dr. H. C. Newman's statement (*Journal*, June 14, p. 1417) succinctly and authoritatively puts it, "Whereas I agree that the vaporizer might be modified to possess bigger ports and pathways, the matter is not quite as alarming as has been made out." We accept this appraisal as being based on accurate measurement, and at realistic flow rates. Even if flow rates of 80 litres a minute or more do occur, they can only be momentarily sustained.

Dr. John Bullough in his latest letter (*Journal*, August 23, p. 510) has not only attempted to restate his case but has ingeniously inserted a number of red herrings which may confuse the issue further and possibly trap the unwary. Coughing and straining (which in our practice with halothane is practically non-existent) are largely a matter of forced expiration, and therefore as such are mainly a concern of the expiratory valve and *not* the Rowbotham's bottle, which is situated on the inspiratory side of the circuit.

The experiment mentioned of endeavouring to reproduce conditions involving low minute volumes, quoted by one of us (F. R. G.) (*Journal*, June 7, p. 1356) was unsound if only for the reason that a Coxeter-Mushin Mark I unit was used. This machine, as is well known, has been superseded by the Boyle Circle II (used by both of us) because of the former's relatively large areas of dead space, and we are only surprised that the figure given of 2% carbon dioxide was not greater. Work is in progress which will demonstrate clearly, by means of rapid infra-red analysis, that, in a true circle system with halothane, carbon dioxide build-up with low minute volumes is very slight and is of no clinical significance.

We are perturbed at the suggestion that an anaesthetist might be content these days to use an unknown concentration of halothane; surely we have reached a stage in the evolution of this anaesthetic agent that it is imperative to know that we are delivering continuously a safe concentration to the patient? The tendency for halothane to ruin the ether vaporizer of a B.O.C. circle unit has now been shown to be a certainty,[3] and in addition the method carries the great danger of sudden increases in concentration.

Finally, lest it be said that we are unable to see the wood for the trees, a near to resistance-free vaporizer, capable of delivering safe concentrations of halothane in a circle system at theatre temperatures for up to two hours, will be available in a short time.—We are, etc.,

P. J. C. BURTON.
F. R. GUSTERSON.

Worthing.

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Buzzers for Bed-wetters

SIR,—Surely the electrical buzzer is the most expensive and troublesome way of curing bed-wetting (*Journal*, August 23, p. 499). There is another and simpler way which does not seem sufficiently well known. At the Dreadnought Seamen's Hospital I see a large number of young men who wish to go to sea but who are prevented by bed-wetting. They are easily cured by pituitary snuff and strong suggestion. Pituitary snuff inhibits the secretion of urine so that if the patient empties his bladder before going to bed and takes a sniff of snuff he cannot wet the bed because he has no urine left to do so. He is told that bed-wetting is merely a childish habit he has never grown out of, but if he takes the snuff for a few months he will. It is surprising how many cases are successful with this simple routine. No doubt not so dramatic as bells ringing and rising at night to pass water, but much cheaper, simpler, and comfortable.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

Mass Casualties from Nuclear War

SIR,—In the concluding remarks of his presidential address to the Bath, Bristol, and West Somerset Branch of the B.M.A., "Nuclear Warfare and the Treatment of Mass Casualties" (*Journal*, August 9, p. 379), Dr. G. D. Kersley suggests that information must be given to the public to reduce panic about the unknown effects of a nuclear explosion; that people must understand the "stay put" policy; and that the population as a whole must learn some first-aid, home nursing, and self-help. It may not be sufficiently well known that the Women's Voluntary Service is giving information now on these lines to one in five of the women in the country under the W.V.S. "One-in-Five" scheme. Specially schooled W.V.S. speakers give the first two short talks, based on information contained in the Civil Defence manual, and drawn up in full consultation with the Home Office: "How to Protect Your Home and Family," explaining simply and clearly about the after-effects of a nuclear explosion and how they could be lessened by simple precautions; and "How You Would be Cared for—How to Try to be Independent," explaining the extent of the help which the Civil Defence Corps could give, and how by applying their own practical knowledge women could provide much of this help for themselves. It also impresses upon them the importance of "staying put" in their homes, if asked to do so, however damaged those homes might be.

The third talk, "How to Care for a Sick Person at Home," is given by trained nurses and specially nominated members of the St. John Ambulance Brigade, or St. Andrew's Ambulance Association, and the British Red Cross Society. It was drawn up by W.V.S. with the help of St. John Ambulance Brigade, the British Red Cross Society, Queen's Institute of District Nursing, and the Ministry of Health, and explains very simply how it is possible to care for someone sick in a badly damaged home, how to improvise where necessary, and how to do the best under any circumstances until skilled help arrives.

The talks are primarily designed for the ordinary housewife who does not belong to any special organization. It

is hoped that the practical knowledge which is contained in them would give her some measure of assurance in a nuclear disaster. Small groups of women are meeting in their own homes, at their work, in village halls, and other convenient places to hear the talks, which each lasts about half an hour and which are followed by time for questions. There is nothing to pay, and women are not asked to join any organization, although those wishing for more information are advised to join the Civil Defence Corps.—I am, etc.,

London, S.W.1. MARGUERITE M. HAMMOND,
Joint Head, "One-in-Five" Department,
Women's Voluntary Service for Civil Defence.

SIR,—Dr. G. D. Kersley's paper on this subject (*Journal*, August 9, p. 379) is illuminating, but I suspect it will not produce the effect he apparently desires. The author claims that, with proper preparation, much could be done to alleviate the effects of nuclear warfare on Britain. However, careful examination of his proposals forces one to the following conclusions:

(1) *The schemes proposed are based on impossible estimates of what can be done by one doctor in 24 hours.*—Ahern[1] is quoted as authority for the statement that a filter unit with 10 doctors can sort 6,000 patients and perform urgent surgery on 1,200 of these in 24 hours, allowing 2 minutes per examination and 9 minutes per operation. Now $2\times6,000+9\times1,200$ minutes adds up to 380 hours; that is, each doctor will have to work 38 hours in the 24, which is nonsense. In the same paper Ahern says that one surgeon can categorize 3–4,000 patients in 36 hours. This can only mean that this surgeon examines patients at the rate of one every 30–40 seconds for 36 hours, without pause.

(2) *Our medical services will be disrupted if these schemes are put into effect fully.*—A 10-megaton bomb is stated to produce 110,000 untrapped casualties in a city of a million inhabitants. Of these, 50,000 are serious and two-thirds of them will need hospitalization. Let us accept Ahern's claim that a unit with 10 doctors can "filter" 6,000 casualties in 24 hours and Drummond's statement[2] that three doctors can cope with 100 serious surgical cases in hospital. A simple calculation shows that, to deal with the effects of one H-bomb on such a city, 1,183 doctors will be required. Suppose we follow this estimate to its logical conclusion. We may regard as a potential target any town with a population of over 100,000, and there are 20 million people living in such towns in this country. Since the blow delivered is likely to be adapted to the size of the target, we can assume that the number of casualties in each town will be roughly proportional to the population and that the medical services required will be similarly proportional. We therefore need $20\times1,183$, or 23,660, doctors to be ready to deal with the initial onslaught. Since there will be no time to locate and evacuate 23,000 doctors to their action stations in the brief hour or so left to us after we are warned that the missiles are on their way (and this is the first we shall hear of hostilities), it follows that half the medical profession must leave our large towns in the near future, and the sooner the better, and wait indefinitely at sites 20–30 miles (32–48 km.) away. Since, as we have seen, Ahern's estimate is hardly reliable, we shall need a correspondingly larger proportion of the medical profession to be so evacuated. The effect on our medical services can be imagined.

(3) *Even if they could be put into effect, these schemes would do little good.*—We are not told how many dead to expect, but there will be 150,000 serious casualties per million of population attacked. Of these, 100,000 will be trapped and presumably abandoned. Of the 50,000 untrapped, a third will be abandoned because *under these conditions* there will be no facilities to treat their injuries. Two-thirds will be sent to hospital requiring surgery. Now from Whitney's estimates[3] it is seen that 50,000 serious casualties will need over 10,000 pints (5,700 litres) of blood in the first three days, so we can assume that any surgery undertaken will be effectively without the aid of blood. Anaesthesia will necessarily be of the sort which can be undertaken by medical personnel without special training or by nurses. Asepsis will be of the most primitive kind. It would not be pessimistic to expect a 30% death rate in these circumstances. The net survival, then, of the 150,000 serious casualties will be about 22,000, or one in seven. This is hardly reassuring and does not justify Kersley's optimistic outlook.

(4) *The schemes ignore major factors almost inevitable in a nuclear war and which will prevent them from being carried out.*—No allowance has been made for further waves of assault with nuclear weapons. No allowance has been made for devastation by extensive fall-out, and that this is likely is suggested by the American admission[4] that nuclear weapons have been altered in a way that would increase local fall-out. No allowance is made for breakdown of transport, communication, electricity, or water supply, and none for epidemics or panic. Even the possibility that the rescue services might be unexpectedly efficacious is not envisaged, since the medical services would then be overwhelmed with some of the two-thirds of the casualties who would otherwise have remained trapped.

Many of us are put in a dilemma by such schemes. If we reject them as so much nonsense, we may be accused of refusing to plan to help the victims of an approaching disaster. On the other hand, if they are accepted by any large section of the medical profession and there was extensive participation by the profession in Civil Defence organization, this would certainly revive the illusion now held by few that an effective answer exists to nuclear weapons, that such a war would not be so terrible after all, and that the individual citizen has a good chance of surviving. Such beliefs are false, and to help to spread them is irresponsible, to say the least. Widespread appreciation of the realities of nuclear warfare is the surest safeguard against such a war. We must be on our guard, therefore, against being led by humanitarian considerations to approve of schemes which will blunt this appreciation and thereby bring about the very thing we most wish to avoid. If there is an answer to this threat, it cannot lie in plans which bear no relation to reality. If, for reasons of their own, statesmen wish to foster this illusion, let them take the responsibility for it and let them do it without help from us.—I am, etc.,

Harrow. M. C. BERENBAUM.

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Hypno-anaesthesia

SIR,—We have read with great interest the leading article in the *Journal* of September 13 (p. 682) which reviews the role of hypnosis in medicine and surgery and recommends a more extended employment. The point that we noted with particular attention was the suggestion that clinics could be formed in the larger hospitals to use and study hypnotic techniques in suitable cases.

The two hypnosis societies which we have the honour to represent were founded about six years ago, and together now have a membership of over a thousand medical and dental practitioners, the great majority of whom have attended specially organized courses of instruction in hypnotic techniques. Regular meetings have been held by both bodies at which papers have been read on hypnosis by authorities in various branches of medicine and surgery. Recently we have felt that further progress could best be advanced by the organization of a clinic specializing in hypnotic techniques, and a joint committee of both societies has been exploring the possibilities. Contact has been made with public bodies, the representatives of which have received us with sympathetic interest. The ideal is, as your leading article suggests, to work under the aegis of a large hospital, but a great practical difficulty has been to secure the necessary accommodation. If any such hospital can give us the necessary accommodation we are prepared to furnish the appropriate medical and dental staff from our members, who would be prepared to work on a voluntary basis, at least in the early stages until the value of hypnotic techniques had been amply demonstrated. In this connexion it is important for the practitioner to recognize the limitations as well as the possibilities of hypnosis. An alternative method would be to open a clinic in a central area of London, and, although this presents some financial problems, they are not incapable of solution: nevertheless direct attachment to a hospital represents the method of choice.

There is no doubt at all that a knowledge of hypnotic techniques is essential to a properly equipped doctor or

dentist. Probably for practical reasons (e.g., the congested curriculum) postgraduate instruction in the pre-registration period would be most suitable for the medical practitioner, and some similar method could be devised for the dental surgeon.—We are, etc.,

WILLIAM MOODIE,
President, The Hypnotherapy Group.
E. E. WOOKEY,
President, Dental and Medical Society for the Study of Hypnosis.

"Sytron"

SIR,—In the note on sytron under the heading "To-day's Drugs" (*Journal*, August 30, p. 562) it is stated, "This substance produces diarrhoea in about 25% of patients treated with it." If this is based on Dr. C. F. Herridge's comparative study of ferric chelate and other iron preparations (*Journal*, July 19, p. 140) I should like to point out that he used a preparation of sodium ironedetate containing 71 mg. elemental iron per 8 ml. (2 teaspoonfuls) and administered this dose b.d. or t.d.s. to 10 children. He reported diarrhoea in 3 of these patients—2 transitory and 1 possibly not entirely due to the drug—but expressed the opinion that his dosage could probably be reduced and still give adequate haematological response, with fewer side-effects. The preparation which has been made generally available (sytron) contains sodium ironedetate equivalent to 55 mg. iron in 8 ml. and the dosage recommended for children is ½–1 teaspoonful t.d.s.; experience has shown that this dosage produces adequate response and is better tolerated than the much larger one used by Dr. Herridge.—I am, etc.,

C. BEAVEN,
Medical Service Department, Parke, Davis & Co. Ltd.

Hounslow.

Deluge of Advertisements

SIR,—Dr. B. J. Maxwell's figure of seven and two-thirds pieces of pharmaceutical literature per practitioner in one day is far from being a record (*Journal*, August 2, p. 329). Were it a matter for pride, I should boast of the 30 delivered one day to my home in Sussex. Many had to be redirected for the second time, having been sent to the wrong address in Malaya, some for the third time. Since one hospital complained that my "correspondents" had not been notified of my change of address, I sent out 37 circulars of my own requesting pharmaceutical firms not to bother me with preparations which had no use in anaesthesia. I received five replies, expressing all degrees of concern at my annoyance, and one Swiss firm was frank enough to explain they worked on the "all-or-none" principle. When I firmly declined to receive their advertisements, they discovered it was after all possible to oblige a potential customer.

I have no figures to show accurately the result of my campaign, but I should say the "flow rate" has decreased about 50%. One or two firms appeared to attack me with renewed vigour when they learned my latest address, and I should be delighted to co-operate with other members of the profession in compiling a black list of these people. On the other hand, it gives me pleasure to record the outstanding courtesy of Messrs. May and Baker, both here and in England.—I am, etc.,

A. S. GARDINER.

Malaya.

"Flying Ambulance"

SIR,—The portrayal of medical practice on television will remain, no doubt, a controversial subject. Let us give the B.B.C. full marks, however, for a really commendable production, "Flying Ambulance," which portrayed with tact and accuracy some of the problems of general practice in an isolated community off the West Coast of Scotland. It was a most moving tribute to all our colleagues—medical and non-medical—who undertake such service. I hope there will be an early repeat of this programme, because, in common with many others, a "call" prevented my seeing part of it.—I am, etc.,

S. A. HALL.

London, N.18.

Electrified

SIR,—Dr. Robert McCurdy's letter (*Journal*, September 13, p. 691) is a reminder that electrification is no new phenomenon. We have in the R.A.M.C. Historical Museum a massive manuscript autobiography of one Surgeon-General William Cattell (1829–1919). In the 1880's he was serving in Canada and writes as follows:

"The air here and in the States is thought to be more electrical than in Europe, and the dry winter is especially attended by evidences of such, as by sliding the feet on the carpet to charge the body, so you can light a gas jet by the spark from one's finger. Blanche can do this at any time by taking off her shoes and gliding along the carpet for frictional excitement, and she thinks there is nothing uncommon in the power."

Blanche certainly cannot have been wearing nylons in those days!—I am, etc.,

R. E. BARNSLEY.

Crookham, Hants.

SIR,—We in Canada are acquainted with Mr. L. H. Pimm's startling electrical experience (*Journal*, August 9, p. 390), though we are not afflicted during the summer months. In winter, when the temperature on a crispish January morning may be to 10 to 20° F. below zero and the humidity low, nylon snow-suited infants in their fur-clad mother's arms present the human equivalent of cat's fur and ebony rod, so that paediatricians develop a Pavlovian reluctance to pat them affectionately on the head. I suppose the answer would be to earth all babies as soon as they entered the waiting-room, but, so far, guile in persuading someone else to touch the loaded baby first has been my most effective prophylactic.

Incidentally, I have no idea why Mr. Pimm should have been afflicted during an English midsummer.—I am, etc.,

PATRICK C. MACGILLIVRAY.

Fort William, Ontario.

Gray's Anatomy

SIR,—I have read your recent references to *Gray's Anatomy* and its centenary (*Journal*, September 6, pp. 598 and 610) and I have wondered if the following will be of interest to you. Although it has nothing to do with the book it does refer to two of its former editors. My father was the originator of the anatomical tip, "Timothy doth vex all very nervous pupils," and he once told me that Timothy Holmes was not pleased. It does seem remarkable to me that a phrase of no literary merit should have survived for so long (it must be more than 80 years since it was first coined) and have become so widely known; I understand that it is still in use by students of the present day.—I am, etc.,

B. PICKERING PICK.

Sherborne, Dorset.

POINTS FROM LETTERS

Orthopaedic Medicine

Dr. R. T. D. FITZGERALD (Brampton) writes: Dr. T. Logan's comments (*Journal*, August 9, p. 390) on Professor J. H. Kellgren's review of Dr. J. H. Cyriax's *Textbook of Orthopaedic Medicine* are most appropriate. I would remind Professor Kellgren that in his own admirable researches into pain he made most of his deductions following injections. Dr. Cyriax has done exactly the same, and I am sure that his total of more than 20,000 epidural anaesthetics given both diagnostically and therapeutically . . . gives him at least some claim to know what he is talking about. I am not aware that Dr. Cyriax anywhere ignores morbid anatomical studies. On the subject of disk lesions in particular Dr. Cyriax has been in advance of many of the morbid anatomists and surgeons, both in the medical and veterinary world. . . . The method of manipulation advocated by Dr. Cyriax for cervical and lumbar spines is completely foolproof, and is performed by all St. Thomas's Hospital physiotherapists with no harm to any patient (myself included), the reason being that no anaesthetic is used for this painless procedure. The danger of spinal cord lesions arises only in the work of ignorant osteopaths or in the hands of orthopaedic surgeons who manipulate under anaesthesia. . . . Dr. Cyriax's book is of great value to all general practitioners and students particularly in that it teaches diagnosis with a precision and nicety not elsewhere to be found.

Obituary

W. J. A. WEBSTER, M.B., Ch.B., F.R.C.S.Ed.

Dr. William Webster, who had practised in the village and environs of Cradley, in Herefordshire, until his retirement in 1952, died on August 10 in his 83rd year.

William John Alexander Webster received his medical education at Glasgow University, graduating M.B., Ch.B. in 1898. After holding a resident post at the Western Infirmary and a period of general practice in the Lake District, he went to New Zealand to study conditions existing there in the treatment of mental disorder. On his return he decided to take up surgery and was admitted to the F.R.C.S.Ed. in 1910. He became house-surgeon at the West Norfolk and Lynn Hospital and later was appointed honorary surgeon in charge of out-patients at the North Staffordshire Royal Infirmary, Stoke-on-Trent. During this time he was actively associated with Freemasonry in the town and was a justice of the peace and a town councillor at Newcastle under Lyme. It was a surprise and disappointment to his colleagues on the staff at the Infirmary when he announced that he was leaving surgery for a post in the Ministry of Health of an administrative character. At the Infirmary at that time he was regarded as the best diagnostician, medical or surgical, in the hospital. His erudition was very exceptional, and there was no branch of medicine on which he was not well informed. In 1933, after spending some years in retirement at Milverton, in Somerset, he decided to resume the practice of medicine as a general practitioner. He took over a small practice at Cradley, on the borders of Herefordshire and Worcestershire, and for the next twenty years he worked with vigour and enthusiasm to build up a thriving practice.

Dr. C. S. GLASS writes: In the passing of Dr. William Webster we have lost the last of the all-round, first-class doctors. Trained with Sir William Macewen, he was the complete doctor, unknown in these days of specialization. When he was on the staff of the North Staffordshire Infirmary he used to do all his own pathology and bacteriology. The mantelpiece of his room was festooned with culture tubes, and the long table held his two first-class microscopes and all the necessary requisites. He performed all his own surgery either in the patient's home or in his own house, assisted by his wife, and very occasionally in a nursing-home. Many times I have gone over to Newcastle and given an anaesthetic for him while he did mastectomies, gangrenous appendices, prostates, and what have you. He was rather a slow operator, but a very careful and thorough one. He always said that he had seen more patients killed by speed than by being slow and careful. He was indeed an all-rounder. He did the pathology for the North Staffs Royal Infirmary for a time and the eye work at another time when the only eye surgeon was ill during the first world war. He never used the infirmary dressings and instruments, preferring always to prepare his own. I remember on one occasion I got him far out into the country to see a woman with a suspected meningitis. A lumbar puncture was done by candle-light, and we went back and hunted bugs till 3 a.m. As a diagnostician he was splendid: he often spent twenty minutes in getting a history, and if anyone at the North Staffordshire Royal Infirmary was stumped Webster was always asked to see the case and usually had some very useful suggestion to make. I think of the days when we did hernias, appendices, and hysterectomies in the kitchen on a portable operating table and the anaesthetic was by rag and bottle. To the young surgeon he was ever kindly and helpful. He always said that you must operate under supervision, and was always willing to let a houseman have a go while he stood by. To me, as a young doctor, he was an inspiration, guide, philosopher, and friend. I took all my difficulties to him and never in vain. To his colleagues he was very loyal, and he certainly maintained the highest traditions of the medical profession.

G. E. R. B. writes: I was privileged to be associated with Dr. Webster only in the last decade of his life. As a young man entering general practice I considered myself most fortunate to be working with a man of such vast experience and wide knowledge and one who still preserved his truly remarkable flair for diagnosis. He had a prodigious memory, and I have listened on many occasions to him reciting case histories in minute detail dating back to the beginning of the century. His singleness of purpose in pursuing a problem was an inspiration to me, as was also the faith and confidence that he inspired in his patients. When he had his surgery built at Cradley just before the second world war, he incorporated into it what was virtually a one-man pathological department, and spent many hours at the microscope and the bench. He still practised surgery when he could, and on a number of occasions since 1948 I have not only given anaesthetics in patients' homes but helped him to load up his car with all the equipment and instruments, including a portable operating table. He and his wife, who predeceased him in 1956, were held in great esteem throughout the surrounding countryside. To the end, through many months of suffering, he maintained his interest not only in the many medical problems that I could take him but also in the stocking and cultivation of his garden, which he loved so much.

J. W. BROWN, M.D., F.R.C.P.

Dr. J. W. Brown, who was a regional cardiologist with headquarters at the City General Hospital, Sheffield, died at Mount Vernon Hospital, Middlesex, on September 16. He was 61 years of age.

James William Brown was born at Gloucester on January 23, 1897. After serving with the French Red Cross from 1915 to 1918 during the first world war he enrolled as a medical student at the Middlesex Hospital, and qualified M.R.C.S., L.R.C.P. in 1923. He obtained the London degrees of M.B., B.S. in 1924 and proceeded to the M.D. four years later. In 1930 he was elected a Member of the Royal College of Physicians of London, becoming a Fellow of the College in 1942. After qualification he held the appointment of casualty medical officer at the Middlesex Hospital. He was in general practice at Cleethorpes from 1924 to 1931 and at Grimsby from 1931 to 1938, when he became a consultant physician with a particular interest in congenital heart disease. Physician for many years to the Grimsby and Scunthorpe hospitals, he subsequently became cardiologist to both hospitals and to the Lincoln County Hospital. In 1952 he was appointed a part-time lecturer and clinical teacher in medicine in Sheffield University. A member of the British Medical Association for 35 years, he was chairman of the Grimsby Division in 1932–3 and he represented his Division at the Annual Representative Meetings in 1928, 1929, and 1931. He also served on the Consultants and Specialist Committee from 1946 to 1948. He was the author of *Congenital Heart Disease*, a book first published in 1939 and of which a second edition appeared in 1950.

F. M. writes: Dr. J. W. Brown, "Jim" to many of us, died at a comparatively early age, but few have lived a life with more activity and a wider range of interests. His boyhood in Gloucestershire gave him a knowledge of and an interest in all aspects of rural life. Had he not from an early age always been attracted by medicine he would surely have become a great naturalist. This interest in bird, animal, and plant life persisted, and it was always a joy to be with him on a country walk or to show him around one's garden. His zest in these aspects of life was apparent in his photographic work and in his engravings on wood and lino. He had a great appreciation of graphic and decorative arts, and keen critical faculties with books, cinema, and stage. But there was little time for these aspects of life, since medicine always had first call. With himself he was merciless when medical work was concerned. The highest standard was all that he would consider, and he expected others in his profession to be similarly minded.

The fact that he was forthright, outspoken, and confident of his own knowledge did, on occasion, lead to pronouncements that could hurt and were sometimes unforgiven. But to most he will be remembered as a delightful, lovable man, free from any form of affectation and with little time for the outward pomp of this life, cherishing his profession and an active supporter of the B.M.A. In the sphere within which he worked he has left his mark, one that will persist. In the wider sphere of medicine his pioneer work on congenital heart disease culminating in the publication of his book, *Congenital Heart Disease*, brought him an international reputation and will assure him a place among those who lived and worked in the highest traditions of the medical profession.

H. MURTAGH, M.B., B.Ch.

Dr. Harold Murtagh, who had been in practice in Ripponden, Yorkshire, for nearly thirty years, died suddenly on August 29 while on holiday in Cornwall. He was 58.

Harold Murtagh was born on August 20, 1900, and studied medicine at Queen's University, Belfast, graduating M.B., B.Ch., B.A.O. in 1927. Through a family friendship with the late Mr. John Hodgson, who was a surgeon on the staff of the Royal Halifax Infirmary, Harold Murtagh joined the resident staff of that hospital, where he was successively house-physician, house-surgeon, and resident surgical officer. When he had completed these appointments in 1929 he joined the late Dr. J. M. Wrangham in practice in the village of Ripponden in the rural Ryburn valley, where he remained for the rest of his life. Keenly interested in his work as a general practitioner, he held the posts of police surgeon and appointed factory doctor for the valley and was medical officer to Rishworth School. His leisure was devoted largely to fly-fishing and gardening.

N. H. writes: Harold Murtagh was a true rural general practitioner, beloved by all in the wide area he served, where his equable temperament made allowances for the oddities of human nature, and his cheerfulness played no small part in his successful therapy. A patient recently declared that to visit him was in itself a tonic. He was a man of great energy, and his arrival was invariably announced by a cheery whistle, but he wasted no time in the completion of his duties. No wonder that his loss is most keenly felt by all his patients and by his partner. He leaves a widow and a daughter, who is a medical student, and in their loss they will have the sympathy of all his friends and colleagues.

D. JUSTIN DAVIES, M.B., B.S., F.F.A. R.C.S.

Dr. D. Justin Davies, consultant anaesthetist in Leicester, died with tragic suddenness on September 7, when he collapsed during a game at the Leicestershire Golf Club. He was 61 years of age.

David Justin Davies was born on July 26, 1897, the son of the Rev. D. C. Davies. Educated at the University Colleges of Aberystwyth and Cardiff, he completed his clinical training at the Middlesex Hospital, qualifying in 1920. After holding resident posts at the Middlesex, he became an assistant medical officer at one of the Metropolitan Asylums Board hospitals in London. Having graduated M.B., B.S. at London University in 1924, he came to Leicester Royal Infirmary as house-surgeon in that year. Later he married Dr. Lucy Simpson, a daughter of the late Councillor Herbert Simpson, a former Lord Mayor of Leicester, and they set up in joint practice in that city. Becoming interested in anaesthetics, he decided to make that his specialty, and was appointed visiting anaesthetist to Leicester Royal Infirmary in 1933. He gained his D.A. in 1935 and was elected F.F.A. R.C.S. in 1953. He soon became recognized as an anaesthetist of outstanding ability and enjoyed an extensive hospital and private practice. Maintaining a keen interest in clinical matters, he was a most regular attender at meetings of the Leicester Medical Society, of which he had been a vice-president. He was an ex-president of the Sheffield and East Midland Society of Anaesthetists. A keen Territorial, he held the rank of lieutenant-colonel in the R.A.M.C., commanding the No. 9 C.C.S., which went to France in 1939, but he was invalided out of the Service after Dunkirk.

R. McD. C. writes: Dr. D. Justin Davies was a most likable man and extremely popular with all with whom he came in contact; in consequence he had a very wide circle of friends, all of whom will miss very much his genial and engaging personality. The loss of his wife in 1947 was a very great blow, but he was devoted to his daughter, who is now in her final year in medicine, and his interest in her career and well-being came to be the outstanding object in his life. To her is extended the sincere sympathy of his many friends and colleagues in the loss of a loving father. Recently Dr. Davies had been in failing health, but fully realized the import of his physical handicaps. Himself a son of the manse, he took a deep interest in the affairs of the Presbyterian Church in Leicester, of which he was an elder. He developed a most admirable philosophical attitude to life, and was determined to carry on with his work. Nothing gave him more pleasure than a quiet game of golf with his friends, and one cannot help feeling that the end, coming as it did, might well have been the one he himself would have chosen.

J. CATHCART, M.B., Ch.B., D.P.H.

Dr. John Cathcart, who was formerly in practice in Bootle, died suddenly at his home at Chorley, in Lancashire, on August 26. He was 72.

John Cathcart was born on March 29, 1886, in Kells, in Northern Ireland, and studied medicine at Edinburgh, where he graduated M.B., Ch.B. in 1910, taking the D.P.H. in the following year. After holding resident appointments at Stockport Infirmary, the Royal Victoria Hospital, Belfast, and the Barnes Convalescent Home of Manchester Royal Infirmary, he decided to specialize in tuberculosis and became a medical officer at Whiteabbey Sanatorium in Co. Antrim. During the first world war he served in France in the R.A.M.C., being attached for much of the time to the Black Watch. On return to civilian life he held a resident post at Lord Mayor Treloar Cripples' Hospital, Alton, and then joined the staff of the Lancashire County Council as assistant tuberculosis officer, remaining in that employment for twelve years. After further sanatorium appointments he decided to go into general practice and eventually settled at Bootle, where he took part in establishing a group practice. During the second world war his house was destroyed by a bomb, but he continued to practise until three years ago. He leaves a widow.

C. H. BURGESS, M.B., Ch.B.

Dr. C. H. Burgess, who practised for many years in Hoylake, died there on September 1 at the age of 75 years.

Charles Herbert Burgess was born on August 26, 1883, the third son of Dr. Robert Burgess, of Coagh, Co. Tyrone. Educated at the Royal School, Dungannon, and at the University of Edinburgh, he graduated M.B., Ch.B. in 1906. After a period of practice in Doncaster he moved to Hoylake in 1911. During the first world war he served in the R.A.M.C. from 1914 to 1918, mainly in Egypt and Palestine. Returning to Hoylake, he remained in practice there until he retired last March.

In 1908 Dr. Burgess married Meta Jeanette Leitch, who died not long ago. He is survived by a daughter and by a son, who is surgeon on the staff of the Southport General Infirmary.

We are indebted to Dr. J. A. ELLIOT for the following appreciation: Charles Burgess was a perfect example of the

best type of family practitioner—wise, calm, patient, and inspiring. He was a retiring person, and I knew him for years before I knew him well. Thereafter I was privileged to enjoy his friendship and to share work with him. He was a wise and far-seeing person and occasionally gave me remarkably valuable advice, ranging in subject from the value of tinned hams in the summer of 1939 to that of a new car in the following year—just before such a thing disappeared off the market. I learned much from him and found the process entertaining as well as educative. It would be impossible for his friends to forget what he was like. His last illness was borne with stoical and matter-of-fact calm which was not only characteristic but deeply impressive.

T. I. ROWLAND, M.B., B.S.

The death of Dr. Trevor I. Rowland at the age of 31 has been reported from the Solomon Islands. A medical officer of the South Pacific Health Service, he was travelling, accompanied by his wife, on board the Government ship R.C.S. *Melanesian* to pay a routine visit to the isolated Polynesian atoll of Sikiana, when the ship was lost, on or about July 10, with all 60 or so souls on board. So far the body of only one crew member has been recovered.

Trevor Ingman Rowland was born on August 15, 1926, and studied medicine at Guy's Hospital, graduating M.B., B.S. in 1950. After holding the posts of house-physician at the Southern Hospital, Dartford, and to the radiological department at Charing Cross Hospital, he served for two years in the R.A.M.C. Entering the Oversea Civil Service in 1956, he worked for a year in Fiji and was then transferred to the British Solomon Islands Protectorate, being stationed as medical officer on the island of Malaita.

J. D. M. writes: Although his short service in the Solomons was fated to be terminated so abruptly, Dr. Rowland's pleasing personality, his professional competence, and the unstinted hospitality of a home managed more than capably by his charming wife endeared him to his colleagues and friends, and not least to the Solomon Islanders in whose service he lost his life.

R. R. MACNICOL, M.B., Ch.B.

Dr. Roderick R. Macnicol, who died at his home in Edinburgh on September 4 at the age of 87, practised at Taynuilt for fifty years and was well known in the West Highlands.

Roderick Reid Macnicol was born on March 15, 1871, and received his early education at the village school at Dalmally, where his father was in practice, having moved some years before from North Uist. Going on from Glasgow High School to the University, he graduated M.A., M.B., Ch.B. in 1898. After working as an assistant in Oban and then in Blantyre, he was appointed parish medical officer in Taynuilt, and for fifty years he practised in this widely scattered district, which extended from his home far beyond the head of Loch Etive on the one side to the shores of Crevan in the north and over difficult roads to Kilchrenan and Dalavich on Loch Awe.

J. A. C. G. writes: During all his years in Taynuilt Dr. Macnicol looked after his patients both far and near with zeal and skill. Many a time he had to travel for miles in an open boat or on foot and often on horseback. These journeys had to be undertaken in summer and winter, by day and by night, often in wind and rain. He always seemed to enjoy the walking, which he said contributed to his good health. He came to Taynuilt at a time when there were no telephones and the motor-car was unheard of in the Western Highlands. He was a man of even temperament, never perturbed by anything. A fluent Gaelic speaker, he was a great upholder of the language and was a life member of An Comunn Gaidhealach. A good pianist, he was always ready to help, and his talent was much appreciated by everyone.

He never seemed to grow old, and remained young-looking and active to the day of his retirement. Some years after he retired, when he was over 80 years of age, he attended a meeting of the Argyll Division of the B.M.A., of which he was a former chairman, and his colleagues were amazed to find that he had not changed in any way, and was still the same quiet, knowledgeable colleague we had all liked so much when he was in practice in Taynuilt. During the first world war he served for four years in the R.A.M.C. After the war he acquired his first motor-car, to use, as he said, "when there were roads available."

Dr. Macnicol was a real Highland gentleman, with an individuality and a charming personality all his own. He enjoyed his work to the full and never spared himself in fulfilling his arduous duties in the scattered West Highland district which he liked so much. He will long be remembered by his colleagues and his patients and by everyone in the community he served so well.

His wife died many years ago, and he is survived by his daughter, to whom our sympathy is extended in her sad bereavement.

Medico-Legal

CHIVERS CANCER ASSOCIATION IN LOTTERY TROUBLE

[FROM OUR LEGAL CORRESPONDENT]

With certain statutory exceptions lotteries are illegal in England. A lottery is any scheme for the distribution of prizes by the operation of chance, and a raffle is a typical example. The statutory exceptions are not designed to make the path of the lottery promoter smooth.

The Betting and Lotteries Act, 1956, created a new exception in favour of lotteries promoted on behalf of registered societies established for charitable and certain other purposes to allow them to raise money for the purposes of the society. The principal thorn on this rose is that the total value of the tickets sold must not exceed £750, but a branch of a society for the purposes of the Act counts as a separate society.

On September 16 Harold Chivers and the Chivers Cancer Association Ltd., of Southchurch Road, Southend, pleaded guilty at Southend Quarter Sessions to five charges of promoting lotteries on behalf of the Chivers Cancer Association Ltd., with, in each lottery, tickets on sale exceeding £750 (*Manchester Guardian*, September 17). For the prosecution it was said that the association, a company limited by guarantee with the object of raising funds by any lawful means for cancer research and treatment, had registered a number of non-existent branches from which to run lotteries simultaneously. The Act required, however, that to be treated as a separate society the branch must be a bona-fide one, and not just attached to the name of someone who as in this case had only to sign two documents. It was stressed by the prosecution that Mr. Chivers had an excellent character. There was no question of fraud. For the defence it was said that Mr. Chivers had collected £10,000 between 1952 and 1956 for cancer research. Neither he nor Mrs. Chivers had benefited in any way from the lotteries, the prizes for which had been Premium Bonds.

Fines of £50 each were imposed on Mr. Chivers and the company and each was ordered to pay £25 costs, two months being allowed for payment. This case should serve as a warning that, however excellent the object, the promotion of lotteries for the purpose of raising money is beset by very stringent restrictions, the infringement of which carries heavy penalties. It is dangerous to attempt to run a raffle without legal advice.

Vital Statistics

Week Ending September 13

The largest fluctuations in the number of notifications of infectious diseases in England and Wales during the week ending September 13 were decreases of 374 for measles, from 1,977 to 1,603, and 45 for whooping-cough, from 791 to 746, and an increase of 27 for food-poisoning, from 275 to 302.

A further decline in the incidence of measles was recorded throughout the country; the largest falls in the number of notifications were 89 in Lancashire, from 315 to 226, and 66 in Sussex, from 112 to 46. The number of notifications of scarlet fever, 296, were 8 fewer than in the preceding week, and there were no large fluctuations in the local returns. The trends of whooping-cough showed very little change, with the exception of a fall of 50 in the number of notifications in Lancashire, from 119 to 69. 3 cases of diphtheria, the same number as in the preceding week, were notified, and 2 of these cases were notified in Plymouth C.B., where 2 cases were also notified in the preceding week.

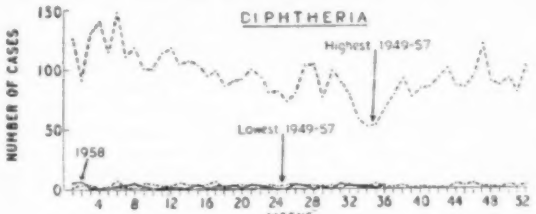
The number of notifications of acute poliomyelitis numbered 62, and these cases were 20 fewer for paralytic and 2 more for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 13 (Leeds C.B. 4, Bradford C.B. 2), Lancashire 12 (Manchester C.B. 5, Liverpool C.B. 3), and Yorkshire North Riding 5 (Middlesbrough C.B. 2).

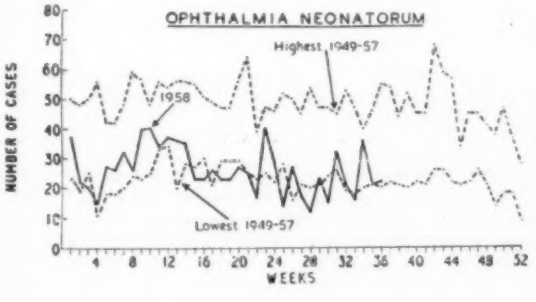
The number of notifications of dysentery, 329, was 13 more than in the preceding week. The largest centres of infection were Yorkshire West Riding 55 (Leeds C.B. 21), London 54 (Bermondsey 13), Lancashire 44 (Liverpool C.B. 18), Nottinghamshire 19 (Basford R.D. 10), and Warwickshire 19 (Birmingham C.B. 10).

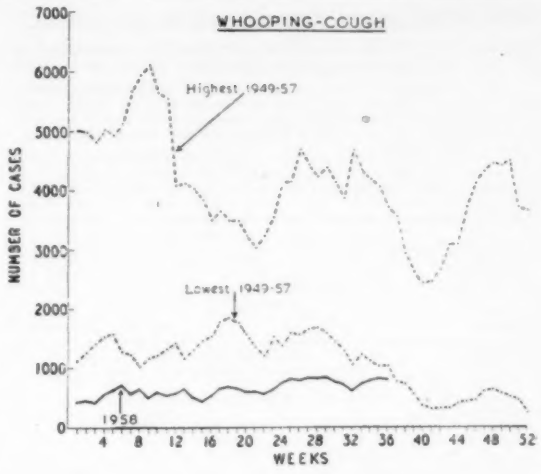
The largest outbreak of food-poisoning was 20 cases in the metropolitan borough of St. Pancras.

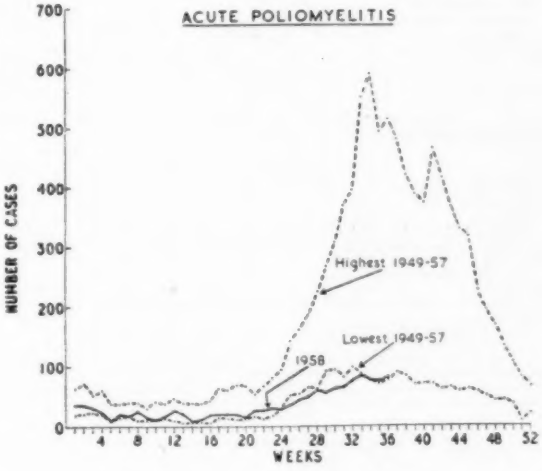
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









X-rays in Industry

At the end of 1957 about 400 factories in Britain were using radioactive isotopes, and over 100 were operating *x*-ray apparatus, according to the Annual Report of the Chief Inspector of Factories for the year.[1] The chief hazard to health at present is thought to be when sealed sources such as strontium-90 and thallium-204 are used to emit beta rays. The hazard occurs mainly when the machine is being dismantled for maintenance or to remove the source. Isotopes used for radiography are thought to be a greater hazard than *x* rays. In most cases when *x*-ray operators have received an overdose it has been an accidental and isolated occurrence. Luminizing factories pose special problems. One is that the luminizer may often be a young woman who has had no scientific education, and therefore "it is difficult for her to grasp the real nature of the hazard." The following example is recorded of how badly a luminizing shop can become contaminated:

> "The linoleum top of the desk was found to have surface contamination 60 times greater than the recommended maximum; the facing edge of the luminizer's bench 150 times; the lampshade 80 times; the seat of the luminizer's chair 60 times; the back of the seat 40 times; and the cover of the log book 60 times."

At most establishments the employees are highly skilled technicians aware of the hazards, "although even among these workers dangerous practices sometimes occur."

[1] *Annual Report of the Chief Inspector of Factories for the Year 1957*, cmd. 521. H.M.S.O., 5s.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 6** (No. 36) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	3	0	1	0		1	0	7	0	
Dysentery ..	316	36	135	11	11	220	28	136	10	8
Encephalitis, acute	1	0		0		2	1		0	
Enteric fever:										
Typhoid ..	5	0	1	0	1	6	1	0	1	1
Paratyphoid ..	9	1	0	1	1 (B)	12	0	2	0	
Food-poisoning ..	275	30	17	1		223	20	31	1	
Infective enteritis or diarrhoea under 2 years				16	32				6	28
Measles*	1,977	118	17	20	21	2,073	53	28	26	8
Meningococcal infection	10	0	13	0		31	7	6	1	1
Ophthalmia neonatorum	22	3	3	0		20	2	1	0	
Pneumonia† ..	144	9	105	1		206	11	139	3	
Poliomyelitis, acute:										
Paralytic ..	60	1	20	1	3	158	12	12	13	4
Non-paralytic ..	20	1				121	6			
Puerperal fever‖	188	19	12	0	1	218	41	6	1	
Scarlet fever ..	304	19	55	7	8	272	18	51	14	14
Tuberculosis:										
Respiratory ..	412	44	91	13		502	45	118	22	
Non-respiratory	73	4	12	3		69	2	11	4	
Whooping-cough ..	791	45	100	61	6	1,013	75	97	2	25

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	0	0		0			0	0		
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	1	0	0		0	3	0	1
Influenza	4	0	1	0	0		0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	3		
Pneumonia ..	340	26	12	8	3		12	11	10	4
Poliomyelitis, acute	4	0		0	0		2	0	0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	70	7	8	1	1		6	6	1	2
Non-respiratory		0	0	0	0		0	0	0	0
Whooping-cough ..	0	0	0	0	0		0	0	0	0
Deaths 0–1 year ..	284	19	23	4	8		22	35	4	15
Deaths (excluding stillbirths) ..	7,878	622	477	79	141		668	529	94	154
LIVE BIRTHS ..	13,658	1116	961	191	361		1124	894	204	383
STILLBIRTHS ..	323	26	19				21	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‖ Includes puerperal pyrexia.

Medical News

Travelling Fellowships.—The Medical Research Council invites applications for travelling fellowships in medicine and medical science, to be awarded for the academic year 1959–60. These fellowships are intended for graduates resident in Britain who have had some training in research work in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad before taking up appointments for higher teaching or research in the United Kingdom. Fellowships held in the United States will provide maintenance allowances at rates varying from $3,000 to $5,000 per annum, according to individual circumstances, and travelling expenses will also be supplied. Further particulars of these fellowships and forms of application may be obtained from the secretary, Medical Research Council, 38, Old Queen Street, Westminster, S.W.1, to whom the completed form should be returned not later than October 31.

Parkes Weber Collection.—Dr. F. PARKES WEBER has presented to the Wellcome Historical Medical Library, London, the remarkable collection of manuscript notes, reprints, and case reports of rare diseases which he has brought together in the course of his long and distinguished career as a physician and medical writer. Dr. Parkes Weber was born in 1863, and his books, *Rare Diseases and Some Debatable Subjects* (2nd ed., 1947) and *Further Rare Diseases* (1949), were based on a selection of this material. A general index to the "Parkes Weber Collection," as it is to be known, will be prepared by the Wellcome Library, where in due course it may be consulted, together with the original records and reports.

"Gray's Anatomy."—On September 18 at the Stationers' Hall, London, the directors of Messrs. Longmans, Green, and Company, the publishers of *Gray's Anatomy*, gave a dinner to celebrate the centenary of this famous textbook's first appearance. The guest of honour was Professor T. B. JOHNSTON, senior editor of the centenary edition. The company which assembled in the finely restored Stationers' Hall was a judicious mixture of anatomists and other medical folk, and of those concerned with the book's production. Mr. WILLIAM LONGMAN, who proposed the toast to *Gray's Anatomy* and its editors, said the occasion was not so much the centenary of a book as the centenary of the birth of an idea of a book. Longmans had always been interested in medical books; in their 1725 book list 44 of the 520 titles were medical, three of them works on anatomy, including Cheselden's, which saw 13 editions between 1713 and 1792. Professor JOHNSTON, replying on behalf of himself and his fellow editors, Professor D. V. DAVIES, of St. Thomas's, and Professor F. DAVIES, of Sheffield, sketched the origins and later progress of *Gray's Anatomy*. It was a wonder it had survived, he said. It had to weather a damaging first review; its first publishers went out of business after the second edition; and Gray himself died of smallpox in 1861 at the early age of 34. Credit for its survival was due to Timothy Holmes, who edited the next seven editions between 1863 and 1880. Professor JOHNSTON ended by thanking all those who had contributed to the present centenary edition.

Guy's Hospital.—On September 19 LORD NUFFIELD, president of Guy's Hospital, laid the foundation stone of the hospital's new surgical block (see *Journal*, September 28, 1957, p. 773). The block is an eleven-story building, designed by Mr. A. S. GRAY, F.R.I.B.A., with the help of Mr. PAUL G. BURT, of Chicago. Its cost is put at about £2.25m., and it is expected to be finished in two years' time. Speaking at the foundation ceremony, the MINISTER OF HEALTH, Mr. Derek Walker-Smith, paid tribute to Lord Nuffield's great generosity to Guy's. The new building, he went on, was a striking manifestation of the steady

growth and acceleration of the Government's hospital building programme. These projects represented in terms of money £10m. in 1955, £13m. in 1956, £18m. last year, £20m. this year, and £22m. next year.

Medical Society of London.—Sir CECIL WAKELEY, president of the Medical Society of London, appeals on behalf of the society for the loan of portraits of former presidents so that they may be photographed for permanent record. The society has an almost complete list of its presidents since its foundation in 1773, and would be glad to hear of portraits of any of the following:

John Millar, M.D., 1773	Theophilus Thompson, M.D., F.R.S., 1844
George Edwards, M.D., 1779	Walter Cooper Dendy, 1846
George Pinckard, M.D., 1811	Edward Headland, 1854
Thomas Walshman, M.D., 1817	Francis Hird, 1857
David Unwins, M.D., 1821	William Hughes Willshire, M.D., 1858
William Shearman, M.D., 1823	Francis Sibson, M.D., F.R.S., 1862
John Burne, M.D., 1831	Peter Marshall, 1869
John Whiting, M.D., 1835	John Cockle, M.D., 1879
Thomas Egerton Bryant, 1837	
Leonard Stewart, M.D., 1839	
George Pilcher, 1842	

Information about portraits of these past presidents should be sent to Sir Cecil Wakeley at the Medical Society of London, 11, Chandos Street, Cavendish Square, London, W.1.

Medical Photography.—The ninth annual conference of the Medical Group of the Institute of British Photographers was held at the Royal College of Surgeons, Lincoln's Inn Fields, from September 18 to 21. Sir JAMES PATERSON ROSS, P.R.C.S., opened the conference, which then proceeded to discuss such topics as the routine production of colour prints, the design of hospital photographic departments, the relationship between the medical photographer and his medical colleagues, and the presentation of demonstration panels. During the conference the Group held its annual meeting, under the chairmanship of Mr. NORMAN K. HARRISON. On the last day there were demonstrations of the Land polaroid camera and of the photography of dermatological and orthopaedic conditions.

Changes at the Ministry.—Dr. G. A. CLARK, one of the two deputy chief medical officers at the Ministry of Health, is retiring on September 30. He will be succeeded by Dr. DANIEL THOMSON.

COMING EVENTS

Institute of Dermatology.—Semi-permanent exhibition, October 1–28, on "The Sweat-retention Syndrome."

Casualties Union Day.—Casualties Union is holding a civil rescue contest (starting 11 a.m.) and the finals of its annual open competition in first aid and diagnosis (starting at 2 p.m.) on October 5 at the George Cohen 600 Group Depot, Wood Lane, London, W.12. Tickets (2s. 6d.) are obtainable from Miss E. E. JOHNSON, 8, Woodcote Park Avenue, Purley, Surrey.

London Hospital.—Old Students' dinner, October 9, at the Trocadero. Tickets 37s. 6d. (27s. 6d. for those qualified less than five years) from Dr. R. R. BOMFORD, London Hospital, E.1.

Glasgow Graduates in Yorkshire.—Annual dinner, October 17, in the senior common room, Leeds University. Details from Mr. JAMES WISHART, 33, Manor Row, Bradford, 1.

Leeds School of Medicine.—Annual dinner of past and present students, October 31, at the Griffin Hotel, Leeds. Details from the hon. secretary to the medical dinner, Leeds Medical School, Leeds, 2.

Hand Clubs.—The Hand Club of Great Britain and the Second Hand Club are holding a meeting on November 22, from 10 a.m. to 4 p.m., at the Royal College of Surgeons. Any surgeon interested who would like to speak or attend should write to Mr. GRAHAM STACK, 150, Harley Street, London, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, September 29

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. H. J. B. Atkins: Fibroadenosis of the Breast; 6.30 p.m., Mr. R. F. Guymer: Surgeon and the Injured Worker.

Tuesday, September 30

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor C. J. Kaplan: An Appraisal of Conservative Therapy in Skeletal Tuberculosis.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.30 p.m., Mr. R. Belsey: Carcinoma of the Oesophagus.

ROYAL STATISTICAL SOCIETY.—At New Small Lecture Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. Tizard: Prevalence of Mental Defect.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. F. Swann: Vertebral Arteriography.

Wednesday, October 1

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Care of the Mentally Retarded Child. Dr. S. Yudkin: Paediatric Aspects of the Care of Mentally Retarded Children; Miss Jacqueline Grad: Home Care of the Mentally Retarded Child.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Fungi as Saprophytes and Parasites.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Sir Russell Brock: Surgical Treatment of Pulmonary Stenosis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. A. Jeanes: clinico-pathological conference.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. W. N. Mascall: Gonococcal Urethritis.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Medical School, Manchester University, 4.30 for 5 p.m., "Hashimoto's Disease." Dr. R. W. Luxton: Clinical Aspects. Dr. Deborah Doniach: Immunological Aspects.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Dr. Wilfrid Oakley: Surgery in Relation to Diabetes; 6.30 p.m., Mr. D. J. Waterston: Surgery in the Newborn.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At General Infirmary at Leeds, 8.30 p.m., Dr. Michael Johnstone: Respiratory Function During Halothane Anaesthesia.

Thursday, October 2

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. H. R. S. Harley: Subphrenic Abscess.

ROYAL SOCIETY OF HEALTH.—At Town Hall, Colchester, 10 a.m., Dr. J. D. Kershaw: Practical Integration of Health Services; Mr. W. A. Rapier: New Houses for Old: An Experiment in the Modernization of Ancient Houses.

Friday, October 3

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Dowling: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. E. H. Hudson: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners by Dr. Norman Hulbert: Blood Disorders in Association with Ear, Nose, and Throat Diseases.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. R. B. Welbourn: Surgery of the Adrenal Glands.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. George Somerville: Changes in Psychiatric Disorders During the Past 25 Years.

Saturday, October 4

ASSOCIATION OF CLINICAL BIOCHEMISTS.—At Royal College of Surgeons of England, 9.30 a.m. and 2 p.m., scientific meeting (with Association of Clinical Pathologists) including symposium on quantitative paper chromatography; 5 p.m., annual general meeting.

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Preston, 2 p.m., annual general meeting.

Sunday, October 5

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main hospital building, lecture-demonstration for general practitioners. Clinical demonstration by Professor C. E. Dent: Dwarfism. An Obvious Feature Sometimes of Diagnostic Importance.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Armitt.—On September 11, 1958, at Farley House, Farnborough, Hants, to Dr. Marion (formerly Jenkins) and Dr. J. M. Armitt, a sister for Gillian—Rosemary Ann.

Clements.—On September 15, 1958, at Poole, Dorset, to Sheila Mayer, wife of Dr. P. W. Clements, a brother for Gillian and Stephen—Christopher.

DEATHS

Ker.—On September 3, 1958, at Halstead, Essex, William Perceval Ker, M.R.C.S., L.R.C.P., aged 83.

Laslett.—On September 6, 1958, at 1, Albert Road, Farnworth, Bolton, Lancs, William Henry Laslett, *M.C.*, M.B., Ch.B.

Mackenzie.—On September 8, 1958, at the Royal Infirmary, Edinburgh, John Cosserat Mackenzie, M.B., Ch.B., of 67, Mountcastle Drive South, Portobello, Midlothian.

Macnicol.—On September 4, 1958, at 97, Greenbank Road, Edinburgh, Roderick Reid Macnicol, M.B., Ch.B., late of Taynuilt, Argyllshire, aged 87.

Rutherford.—On September 2, 1958, Henry Ireland Gascoyne Rutherford, M.B., B.Ch., of 100, Widdicombe Way, Moulsecoomb, Brighton, Sussex, aged 73.

Schonberger.—On August 12, 1958, Elisabeth Schonberger, M.D., of Greenbanks, Springwell Road, Durham.

Webster.—On August 10, 1958, in a nursing-home, William John Alexander Webster, M.B., F.R.C.S.Ed., of Redbrook Gate, Cradley, near Malvern, Worcs, aged 82.

Wilson.—On August 27, 1958, Fergus Falconer Wilson, M.B., Ch.B.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Toxic Effects of Mersalyl

Q.—*What are the toxic effects of mersalyl therapy, and how should they be treated?*

A.—The most serious toxic effect of mersalyl therapy is heart failure. Mersalyl is a compound of mercury, and mercury has long been known to combine with sulphydryl groups. Compounds containing sulphydryl groups indeed are known as mercaptans because they capture mercury. Mersalyl can combine with sulphydryl groups in the heart and cause arrest. Mersalyl is given by intravenous injection or by intramuscular injection. The risk of causing cardiac arrest is much greater when the intravenous route is used, and for this reason mersalyl should always be given intramuscularly. Dimercaprol is of value in treating the toxic action on the heart, but it must be given immediately there are signs of failure. For example, in the heart-lung preparation of the dog it is possible to cause cardiac arrest by injecting mersalyl and then to restore the beat by injecting dimercaprol. Dimercaprol contains sulphydryl groups which dislodge the mercury from its attachment to the heart. To-day, however, the newer diuretics, particularly chlorothiazide, should be used in preference to mersalyl, for they are much less toxic.

E.C.G. in Angina of Effort

Q.—*What further information may be gained from an E.C.G. in a patient who gives a clear-cut history of angina of effort?*

A.—The electrocardiogram varies in the presence of a clear-cut history of angina of effort. Sometimes definite evidence of myocardial infarction with deep muscle damage is seen, while in other cases the electrocardiogram shows the damage to the muscle to be less serious. Another group of patients shows slight or no evidence of cardiac damage in the resting electrocardiogram, and an electrocardiogram with exercise is necessary to demonstrate the lesion. If the electrocardiogram is normal, both at rest and on effort also, the diagnosis should be questioned. In general, therefore, the electrocardiogram confirms the clinical diagnosis and amplifies it by indicating the degree of muscle damage and also its anatomical site.

The crux of the question, however, lies in the interpretation of the words "clear-cut." Angina of effort is perhaps the most pathognomonic of all cardiac symptoms; it is certainly more so than the isolated pain of cardiac infarction, which may be simulated by pulmonary embolus, dissection of the aorta, and other conditions. In the anxious patient, however, it may sometimes be difficult to disentangle the organic from the functional symptoms suggesting angina of effort, and it is here that the electrocardiogram is of special value.

Inadequate Personality

Q.—*What is the definition of an inadequate or immature personality? Is this a permanent disability, or is it possible to help an adult affected by this handicap?*

A.—An inadequate or immature personality characterizes the individual who is unable (or unwilling) to adapt himself to the everyday demands of his setting in life. The disability is usually due to a mixture of constitutional and environmental influences. Nevertheless, it is seldom easy to lay down the precise responsibility of nature or nurture. It is possible to help the condition and often to help substantially. Much depends upon the patient's age, his capacity for co-operation, his circumstances and general health, and also upon the opportunities for obtaining the requisite professional advice and treatment.

The first step is to find out the nature of the disability. There may be intellectual inadequacy and consequent difficulties in education, or social maladaptation because of personal anxieties and complexes. The immature person is prone to develop neurosis: he compares the achievements of his contemporaries with his own efforts and becomes discouraged. Psychological treatment can relieve this situation and at any rate prevent the spread of the trouble by the accumulation of new symptoms. The patient should be seen by a psychiatrist. He will make a tentative diagnosis, probably using one of the many personality tests, and assess the situation. If he succeeds in establishing a good contact with the patient on a human and personal level, the outlook for later treatment will be much improved.

Glucose Tolerance in Pregnancy

Q.—*(1) Does pregnancy affect the glucose tolerance test; and (2) does the E.S.R. rise in pregnancy?*

A.—(1) Pregnancy does not affect the glucose tolerance test. The finding of reducing substances in the urine in the presence of a normal glucose tolerance test is due either to a lowered renal threshold for glucose or to lactose. (2) The E.S.R. may rise markedly in pregnancy, presumably owing to a decrease in the viscosity of the plasma.

NOTES AND COMMENTS

Tennis Elbow.—Mr. A. H. G. MURLEY (London, W.1) writes: Your expert in the answer to the question on tennis elbow ("Any Questions?" August 16, p. 461) mentions the efficacy of injection of hydrocortisone acetate in this condition. He says that it is useless to expect a satisfactory result unless the injection causes agony. This agony, I feel, is quite unnecessary, as equally satisfactory results can be obtained after local analgesic infiltration of the tender area, provided the hydrocortisone is injected into the area which is tender. Because of the comparatively superficial situation of this area, this is technically quite easy, and by this method the patient is saved a good deal of pain.

OUR EXPERT replies: My experience does not lead me to support Mr. Murley's view. In my hands the preliminary infiltration of a local analgesic makes the subsequent injection of hydrocortisone a less accurate method of giving the patient relief, but, as I stated in my previous answer to the original question, very many different varieties of treatment and of techniques are credited with success in this condition.

Correction.—In the report of Dr. J. Joseph's address at the B.M.A.'s Annual Meeting (July 26, p. 231) the subjects on whom he performed electromyographic studies were described as having "the hands clasped tightly behind the back." This should have read "lightly."

Collected Articles from the "British Medical Journal"

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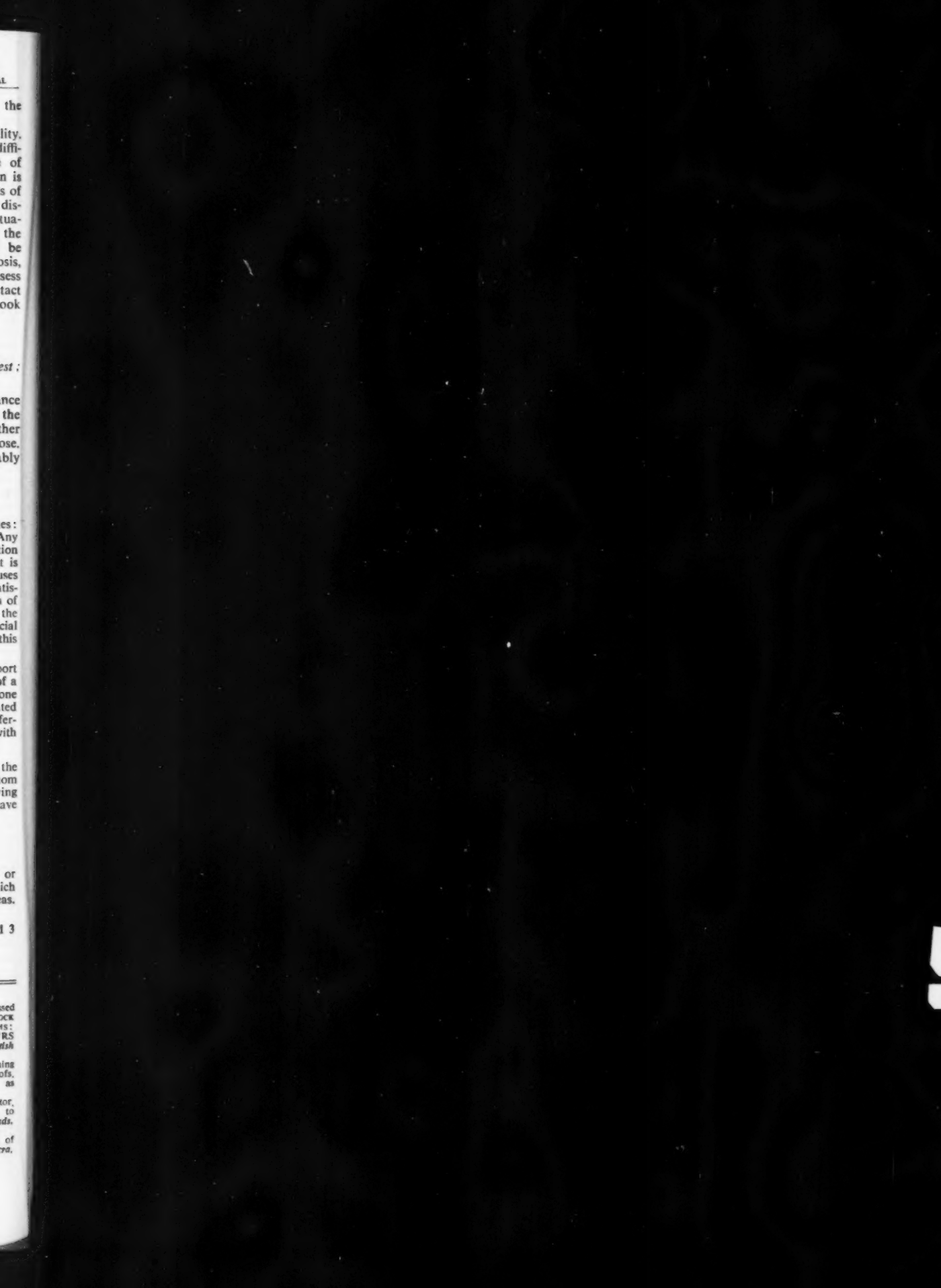
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